THE QUARTERLY REVIEW *of* BIOLOGY

VOLUME 22

1947

Published by

THE WILLIAMS & WILKINS COMPANY
BALTIMORE
U. S. A.

BOSTON UNIVERSITY
COLLEGE OF LIBERAL ARTS
LIBRARY

Chester C. Corbin Library Fund
bound
March 1948

THE QUARTERLY REVIEW OF BIOLOGY

FOUNDED BY RAYMOND PEARL

B. H. WILLIER, *Editor*
The Johns Hopkins University

H. BENTLEY GLASS
Assistant Editor

ADVISORY BOARD

ANATOMY	LEWIS H. WEED	*The Johns Hopkins University*
ANTHROPOLOGY	A. L. KROEBER	*University of California*
BEHAVIOR AND COMPARATIVE PSYCHOLOGY	K. S. LASHLEY	*Harvard University*
BOTANY	IRVING W. BAILEY	*Harvard University*
CYTOLOGY	CHARLES W. METZ	*University of Pennsylvania*
ECOLOGY	THOMAS PARK	*University of Chicago*
EMBRYOLOGY	E. G. CONKLIN	*Princeton University*
EXPERIMENTAL MORPHOLOGY	ROSS G. HARRISON	*Yale University*
GENERAL PHYSIOLOGY	G. H. PARKER	*Harvard University*
	F. O. SCHMITT	*Massachusetts Institute of Technology*
GENETICS	G. W. BEADLE	*California Institute of Technology*
	R. A. EMERSON	*Cornell University*
GEOGRAPHICAL DISTRIBUTION AND TAXONOMY	ALEXANDER G. RUTHVEN	*University of Michigan*
PALEONTOLOGY	ALFRED S. ROMER	*Harvard University*
ZOOLOGY	FRANK R. LILLIE	*University of Chicago*

22

QH
301
F2C1
V.22
1947

CONTENTS

No. 1, MARCH, 1947

Theories of Amoeboid Movement ..... *P. P. H. DeBruyn* 1
The Mechanism of Inhibition of Cellular Activity by Narcotics ..... *William D. McElroy* 25
New Biological Books:
Reviews and Brief Notices 59

No. 2, JUNE, 1947

Organization of the Teleost Blastoderm ..... *Jane M. Oppenheimer* 105
Comparative Physiology of the Thyroid Hormone ..... *Walter Fleischmann* 119
New Biological Books:
Reviews and Brief Notices 141

No. 3, SEPTEMBER, 1947

Experimental Approaches to Problems of Early Development in the Rat ..... *J. S. Nicholas* 179
Maupertuis and the Beginnings of Genetics ..... *Bentley Glass* 196
New Biological Books:
Reviews and Brief Notices 211

No. 4, DECEMBER, 1947

Radiations and Cell Division ..... *Arthur C. Giese* 253
Life Tables for Natural Populations of Animals ..... *Edward S. Deevey, Jr.* 283
New Biological Books:
Reviews and Brief Notices 315
Index 391

VOL. 22, NO. 1 March, 1947

THE QUARTERLY REVIEW of BIOLOGY

THEORIES OF AMOEBOID MOVEMENT

By P. P. H. DE BRUYN

Department of Anatomy, The University of Chicago

INTRODUCTION

IN ADDITION to the rhizopods, many other organisms exhibit movements of protoplasm designated as "amoeboid." Among these are Foraminifera, Radiolaria, and Heliozoa; the plasmodia of myxomycetes; the egg cells of sponges; the spermatozoa of Monoblepharidaceae; the zoospora of many green algae; blood cells, fibroblasts, macrophages, and epithelial cells in tissue cultures; nerve fibers growing out in tissue cultures, and others. The "common denominator" of this heterogeneous group is the fact that in these organisms the movement of protoplasm is accompanied by changes in shape and by progressive motion. The protoplasmic streaming which occurs in plant cells (cyclosis) lacks these characteristics and so such movement is not classified as amoeboid. The protoplasmic movement of Heliozoa and Radiolaria also is frequently set apart as a different type. In the filamentous pseudopodia of these organisms the protoplasmic streaming somewhat resembles that in plant cells, and has been termed by Engelmann (1879) "filament streaming" ("Fädchenströmung").

Even when protoplasmic movements are divided into these three groups, the types of movement classified as amoeboid remain very heterogeneous in character. This diversity is well illustrated by the motion of certain cells in tissue cultures. It has been shown that in tissue cultures of white blood cells, different cell types exhibit different types of movement. These differences are constant and characteristic for the cell type involved, and are most simply expressed in terms of polarization of protoplasmic activity (De Bruyn, 194-, 1945). For example, the movement of the lymphocytes is progressive and the activity of the protoplasm is directionally polarized, i.e., pseudopodia form only in a localized area of the moving cell. In contrast, the protoplasmic activity of the macrophage is not polarized; the pseudopodia arise from all sides of the cell body, and there is no significant progressive motion. However, despite the profound differences in the character of the protoplasmic movement of various organisms, the essential mechanism in all cases may be the same.

Our knowledge of the visible phenomena of the movement of *Amoeba*, myxomycete plasmodia, and white blood cells is well founded. The movement of these organisms is believed to be identical in essential details, and the theories about amoeboid movement have been based almost entirely on observations of these organisms. Other types of protoplasmic movement are considered in this review only as they have a direct bearing upon the several theories.

Our knowledge of amoeboid movement does not go much beyond those phenomena which are microscopically visible. As to what causes such movement, we have only hypotheses. Several theories have been advanced in the course of time. They are all speculative in nature, but with the accumulation of data and with improved methods of study, plus the application of the knowledge produced by the advancing physical sciences, these theories have gradually become more meaningful

and better founded. From now on, important progress is to be expected only from a more experimental approach than has been taken in the past. Efforts to verify the proposed theories experimentally have been few, and not enough physical or chemical data, requisite to an understanding of the mechanism of protoplasmic movement, have been obtained. For instance, it is obvious that any theory of amoeboid movement will ultimately have to take into account the processes of energy production and metabolism. At present, nothing is known about these processes insofar as they are involved in protoplasmic movement. Such investigations will be of special interest because many investigators believe that protoplasmic movement is related to muscular contraction or is even identical with it. The application of new microchemical and microphysical techniques may open the way to the solution of these important problems.

The various theories of amoeboid movement have been greatly influenced by the prevailing concepts of protoplasmic structure. This is not surprising; it has always been evident that the final explanation of the mechanism of protoplasmic movement must ultimately be based on the structure or structural elements of protoplasm. Such other functional cellular phenomena as metabolism, respiration, and secretion may or may not depend on protoplasmic structure, but the phenomenon of protoplasmic movement *must* be so based. For this reason concepts of protoplasmic movement must take into account protoplasmic structure, just as theories of protoplasmic structure cannot ignore protoplasmic movement.

EARLY CONTRACTILITY THEORIES OF AMOEBOID MOVEMENT

The first efforts to explain the mechanism of protoplasmic movement arose from the controversy between Ehrenberg and Dujardin on the organization of Infusoria. Ehrenberg (1830, 1832) maintained that Infusoria, a term which at that time included the rhizopods, possessed organs comparable to those of higher organisms. He based his views on the motility of *Amoeba* entirely on this belief. To him, the pseudopodia were hernia-like protrusions caused by the local weakening of the "body, " through which the contents of the "body" were forced by (muscular) contractions. Dujardin (1835, 1838) opposed the view that Infusoria were differentiated into cellular organs, and found that they consisted of a homogeneous jelly-like mass, for which he proposed the name sarcode. He claimed that his sarcode possessed the properties of extensibility and contractility.

Dujardin thought these inherent properties of the sarcode to be responsible for the changes in form and for the locomotion of *Amoeba*. As he described the phenomenon, the inherent forces of extensibility cause a protusion to be formed and to advance. This protrusion becomes attached to the substratum and subsequently contracts, thus pulling up the rest of the organism.

The role of extensibility in the formation of a pseudopodial protrusion was denied by Ecker (1849), who showed that pseudopodia could also be formed by a process of contraction. He observed that when a pseudopodium forms, a stream of granular material is forced into the growing protrusion. To Ecker this indicated that a pressure was exerted against the growing pseudopodium by that part of the sarcode not taking part in the formation of the pseudopodium. It was his opinion that locomotion resulted from a contraction of the body, by which its contents were forced into the pseudopodium; the pseudopodium then became "body" and in this manner the organism progressed.

After M. Schultze (1861, 1863) identified the sarcode with the protoplasm of other cells, contractility was universally accepted as a general property of living substances, a property upon which was based the ability of protoplasm to move. The mechanism by which the general process of protoplasmic contraction produced protoplasmic flow, change of shape, and progressive movement was later defined more closely by observations which indicated that in cells showing these phenomena the protoplasm was differentiated in an outer cortical layer, which was contractile, and a passive centrally located mass which was brought into motion by the contraction of the cortical layer. This mechanism was first described somewhat vaguely by Brücke (1861, 1862) in his observations of the protoplasmic streaming in the hairs of *Urtica urens*. However, Brücke seemed to believe that the flowing mass was not true protoplasm but a non-living intracellular fluid. Wallich (1863 a, b, c) stated definitely that in *Amoeba*, motion is effected by the contraction of the external sarcode layer (ectosarc), with the internal mass (endosarc) participating only passively in the movement. Wallich also came

to the conclusion that ectosarc and endosarc were not permanent structures but were "mutually convertible one into the other."

The studies of de Bary (1864) on the movement of myxomycete plasmodia led him to a similar view. However, in addition to the movement arising from the contraction of the cortical protoplasm, de Bary believed that there was a movement produced by another force. He thought this force arose from an active expansion at the ends of the plasmodium branches which "sucked" the fluid protoplasm in this direction. To prove the existence of these two forces, de Bary decided whether the driving force in certain branches of a plasmodium was contraction or expansion ("suction"), on the basis of the character of the protoplasmic flow, and then cut these branches. Where he had assumed contraction to be the driving force, protoplasm flowed out at the surface proximal to the cut; the distal surface remained even. When he cut a branch of which he assumed the driving force to be expansion, both cut surfaces remained even. The value of his experiments, however, is weakened by the fact that regardless of whether he thought a contractive or an expansive force to be present, an outflow of protoplasm sometimes occurred at both surfaces.

To give further weight to his theory that contractility produced a protoplasmic flow, de Bary cited experiments by Kühne (1864). This investigator had shown that electric stimulation would cause part of the plasmodium to contract and that this contraction pushed the more fluid granular mass into the neighboring, uncontracted parts of the plasmodium. De Bary also produced experimental pseudopodia in a plasmodium by chemical action (K_2CO_3), an effect which he thought resulted from expansion brought about by swelling. But these experiments do not conclusively prove the existence of an expansive force; pseudopodia may form as a direct result of the chemical action, but the outgrowth does not necessarily occur because of swelling or expansion. De Bary's experiments seemed to produce, primarily, evidence for a contractile force; they were less conclusive as to the existence of an expansive force.

Greeff (1874) ascribed the motility of *Pelomyxa* to the outer layer of protoplasm, contraction of which displaced the centrally located protoplasm, which remained passive. In addition, he noted a difference in consistency, terming the central protoplasm more fluid, or less viscous, than the cortical protoplasm.

F. E. Schulze (1875) was the first to make a detailed study of the currents in the protoplasm of a moving *Amoeba* (*Pelomyxa*). On the basis of his observations, integrated with the idea of protoplasmic contractility, he developed a concept of the mechanism of the progressive movement of *Amoeba*. His observations on the movement of protoplasm in *Pelomyxa* he summarized in a diagrammatic drawing which is reproduced in Fig. 1. In this figure the arrows indicate the direction of movement, their length the rate of movement.

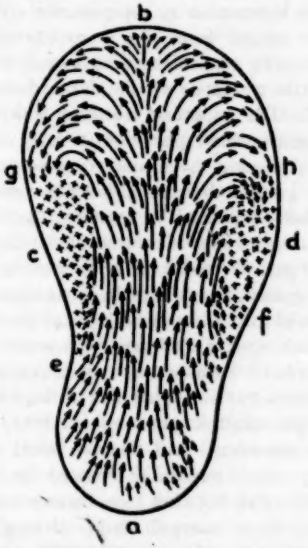


FIG. 1. CURRENTS IN PELOMYXA PALUSTRIS, GREEFF
After F. E. Schulze (1875).

The crosses represent places of rest. It can be seen from this figure that while the organism itself progresses, a part of the protoplasm is not in motion. This mass of protoplasm at rest is located at the sides. From the posterior part of this resting mass, material is continually released and then is taken up into the central forward-moving stream. At the anterior zone of the resting mass, material from the streaming mass is continuously deposited. Thus, material previously released from the posterior part of the resting mass comes later to rest at its anterior part. Schulze observed this displacement and replacement not only at the lateral sides of the moving

organism but also at the upper half. He could not determine whether it also occurred along the lower half, which was in contact with the object glass, but thought this very probable.

On the basis of these observations, Schulze formed his hypothesis regarding the manner of movement and driving force in *Pelomyxa*. Agreeing with Greeff that the cortical layer of the protoplasm is more dense and more viscous than the centrally located protoplasm, he said that the contraction of the cortical layer of the posterior part of the organism at *e, a, f,* pushed the central fluid mass forward. The resting zone at and before *e* and *f* does not expand by the pressure originating from this contraction at the posterior end, since here the cortical layer also is contracted. But at the anterior part the cortical layer is thin and offers little resistance to the forward-streaming material. The important question which arises if one accepts this explanation is: Why does the forward-streaming movement continue once the posterior part of the cortical layer is contracted? This Schulze explained by assuming that there is a continuous transfer of contracted material of the posterior part of the cortical layer into the central streaming mass, and its simultaneous replacement by material from the cortical layer at the sides.

Schulze's observations have been proved essentially correct. Perhaps the most important part of his theory was his explanation of the continuity of the protoplasmic processes involved in progressive movement. All theories based on contractility were temporarily eclipsed by surface tension theories, but after these became untenable, Schulze's ideas emerged again, although in a different form, in Mast's work (1926).

A. Gruber (1882, 1885, 1886) without going into a detailed analysis of the mechanism of amoeboid movement, also was of the opinion that the contraction of the cortical layer at the posterior end is the actual locomotor force. He believed this contraction to be associated with a dehydration of the protoplasm.

The weakness of these early contractility theories was the absence of any accurate knowledge regarding the physical basis of the process of contraction. To most investigators, "contraction" was no more than a somewhat more definitive term for the broad concept of protoplasmic motility, and did not necessarily imply a relation with muscular contraction. M. Schultze, in his work on the protoplasm of rhizopods and plant cells (1863), stated that there is no other expression than the term "contractility" to characterize the inner cause of active motion, and that one was completely in the dark as to the relationship of protoplasmic movement to the contractility of other elements, as, for example, muscle tissue. In contrast, Ecker (1849) believed the motility of sarcode and muscle contraction to be definitely linked. He maintained that sarcode ("undifferentiated contractile substance") was a primitive form of the muscle tissue of higher organisms ("differentiated contractile substance"). He also thought that muscle tissue develops embryologically from undifferentiated contractile substances present in the egg.

Heitzmann's theory (1873) of the structure of protoplasm was an attempt to explain contractility on a morphological basis. To him, protoplasm was not a homogeneous mass, as it was considered by Dujardin, but consisted of a (visible) living contractile three-dimensional reticulum which was imbedded in a non-living non-contractile fluid. It was his view that the fibers increased in thickness at their points of contact and that at these places granular formations occurred (Fig. 2A). Contraction, he said, took place by a transfer of material to the granules from the filaments, shortening the filaments and increasing the size of the granules. This caused the meshes of the network to become narrower, and contraction was the result (Fig. 2B). The obviously homogeneous appearance of certain parts of the protoplasm he explained by assuming that here the reticular framework was stretched to such an extreme that it became invisible (Fig. 2C).

Fromann (1880) also believed in a reticular structure of protoplasm, but he did not try to explain contractility on this ground. Others gave the reticular theory of protoplasmic structure considerable attention, and many accepted Heitzmann's general idea of a contractile framework However, very few investigators expressed themselves as favoring his theory of the mechamism of the contraction.

Leydig (1885) and Schäfer (1883, 1891) held that it was not the reticular framework which was contractile but rather the fluid material in which the framework was embedded (hyaloplasm). Schäfer observed the movement of the white blood corpuscles of the newt (*Triton cristatus*). He succeeded in fixing these in the amoeboid condition with their pseudopodia extended, by instantly

applying a jet of steam to the surface of the cover glass. In such preparations he noted that the protoplasm of the cell body and that of the pseudopodia differed in appearance. In the cell body

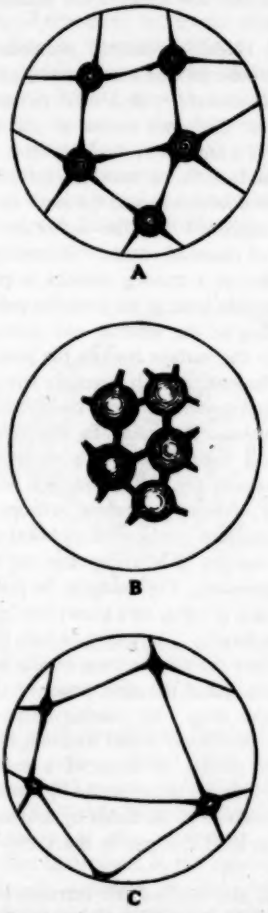


FIG. 2. RETICULAR STRUCTURE OF PROTOPLASM ACCORDING TO HEITZMANN

A, protoplasm at rest; B, contracted protoplasm; C, stretched protoplasm. After C. Heitzmann (1873).

the protoplasm appeared finely reticulated, while in the pseudopodia it was entirely homogeneous. From these observations he concluded that protoplasm did have a reticular structure as claimed by Heitzmann and others, but that the mobility was inherent in the fluid material which surrounded the reticulum. It was his view that this fluid material could actively leave the reticulum and so form pseudopodia.

Engelmann (1879) considered protoplasm to be an aggregate of contractile particles of molecular dimensions, which he called "inotagmen." According to him, protoplasm moves as the result of changes in shape of these elements. He assumed that the particles at rest were rod-like in shape, while when stimulated they contracted into the form of a sphere, these changes in form being accompanied by changes in water content (swelling). He discarded the idea that pseudopodia were formed by a contraction of the posterior cortical layer, and thought such formation resulted primarily from the relaxing of a group of contracted "inotagmen"; that is, by changing from the sphere shape to the rod shape they produced extensions of protoplasm. In essence, this is a mechanism which Dujardin, in his extensibility concept, thought to be in part responsible for the movement of sarcode.

Deficient as were the contractility theories of that time, relatively few dissenting opinions were expressed, of which the more important will now be mentioned. Such criticism as there was arose largely from the lack of certainty regarding the site of origin of the protoplasmic stream in moving cells. The contractility theories were based on the assumption that the protoplasmic stream was created by a vis-a-tergo, and so originated at the end opposed to the direction of movement. De Bary's (1864) observations on the movement of myxomycete plasmodia led him to the belief that other currents arose at the end which was moving forward, as the result of a suction created by an "expansive" force at the end of the pseudopodia. De Bary is not very explicit as to the nature of this expansive force, but from the interpretation of his experiments to prove its existence, he appeared to regard it as a swelling process (see page 3).

Hofmeister (1865) specifically denied that contractility causes protoplasmic movement. According to him, the currents in plasmodia arise only at the advancing end of the pseudopodia; from here the movement of the protoplasm gradually spreads backwards. He rejected de Bary's conception regarding the cause of the currents because they occurred without the changes in shape which he thought should be present if they were produced by an expansive force. To Hofmeister, the protoplasmic movements were based

on differences in water absorption. He assumed protoplasm to be composed of submicroscopic particles whose imbibition of water was continously changing. A transfer of water from one group of particles to another group would result in movement, since an increase of water content would be accompanied by an increase in the volume of the particles.

Sachs (1882) tried to explain the origin of the currents at the end of a pseudopodium by a local disturbance in certain forces which he believed to be active in holding the molecules in a state of labile equilibrium. Such a local disturbance would then spread to places further removed from the site of origin, and a movement would be created which would be directed backward. Just how such a disturbance of equilibrium would produce movement and why such a movement would be directed toward the site of origin, Sachs did not explain.

SURFACE TENSION THEORIES OF AMOEBOID MOVEMENT

When improvements in microscopic technique toward the end of the nineteenth century failed to verify the presence of a reticular framework in protoplasm, the reticular theory of protoplasmic structure had to give way to other concepts. The idea of a continuous framework was abandoned. According to the new theories, the essential structural elements of protoplasm were minute isolated particles dispersed in a homogeneous fluid. These particles were thought to be filaments (Flemming, 1882), granules (Altmann, 1890), or droplets (Bütschli, 1892). Contraction was more difficult to visualize on the basis of these dispersed structural elements than on the basis of a continuous reticulum. Influenced by the new concepts of protoplasmic structure, the theories of amoeboid movement acquired an entirely different aspect. The responsible forces were no longer sought primarily in the protoplasm itself, but outside the cell, or rather, at its boundary.

Quincke's studies (1870, 1877) on the conditions governing the spreading of liquids in contact with other liquids or solids furnished grounds for a new approach to the problem. If three liquids, 1, 2, and 3, are in contact with each other, and the surface tensions at the three interfaces are represented by $\alpha_{1,2}$, $\alpha_{1,3}$, $\alpha_{2,3}$, then it follows from considerations regarding the angles formed by the intersecting interfaces that, for instance, fluid 2 will spread over the interface between fluid 1 and fluid 3, if

$$\alpha_{1,3} \leq \alpha_{1,2} + \alpha_{2,3}.$$

The same is also true if one of the substances 1 or 3 is a solid.

Berthold (1886) considered protoplasm as a liquid. He believed that the spreading phenomena of liquids in contact with a solid substances are essentially of the same nature as the amoeboid movement of a mass of protoplasm on a solid substrate. The fact that a mass of protoplasm on a solid surface does not spread the same on all sides, Berthold explained by the influence of local differences of chemical nature. According to him, the spreading of a moving amoeba is greatest at the anterior pole, least at the posterior pole. While the spreading at the anterior end continues, the adhesion to the surface toward the posterior end gradually lessens, until it becomes free from the substrate and rounds off under the influence of the surface tension. According to this concept, the formation of pseudopodia is a passive process; the pseudopodia are pulled out, not pushed out.

Berthold produced movement in drops on liquid and solid surfaces by the same physical conditions which he thought to be responsible for the movement of amoebae. For example, he brought into motion a drop of water on a glass plate by applying ether vapor locally. According to him, this motion resulted when the adhesion was locally lowered by the condensation of the ether vapor on the surface of the water drop. By placing drops of oil on tap water, previously soiled with oil, he obtained movements similar to those of amoebae. This motion he believed to be caused by locally varying rates of exchange of the fluids by mutual solution, resulting in local changes in the forces governing spreading.

Berthold also studied the currents in drops in which the surface tension was locally altered. He noted the similarity between the currents in such drops (Fig. 3) and those in moving amoebae (Fig. 1). However, he did not believe that the currents in both amoebae and drops were caused by the same mechanism, since the currents in the medium surrounding the drop are not present in the fluid around the moving amoeba. It was his conclusion that the "fountain streaming" in moving amoebae was caused simply by a more intensive spreading in the axis of the cell body than at the lateral parts.

That drops in a fluid medium and on a solid substrate change form and can be brought into motion by local changes in surface tension was also shown later—and more conclusively—by Quincke (1888) and Bernstein (1900). However the theory of amoeboid movement based on such considerations is markedly deficient in that it does not explain the extension of pseudopodia which are not in contact with a solid substrate. To explain the formation of such free pseudopodia, Berthold was forced to assume an entirely different mechanism—a pressure from behind by a contraction of the peripheral protoplasm. Thus he proposed two different mechanisms for essentially the same process.

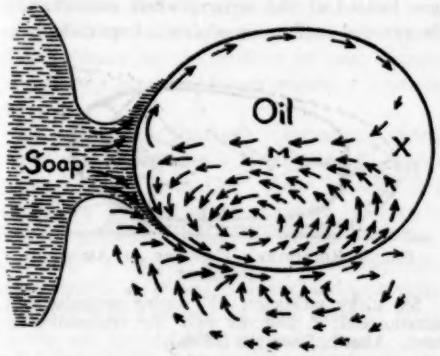


FIG. 3. CURRENTS IN A DROP OF OIL IN WATER AND IN CONTACT WITH A SOAP SOLUTION
After O. Bütschli (1892).

Bütschli (1892) agreed with Berthold that local differences in surface tension were the primary cause of amoeboid motion, but he did not accept that part of Berthold's hypothesis concerned with the mechanism of the movement. Bütschli's views are best understood in the light of his ideas of protoplasmic structure. Studying protoplasm with the finest optical equipment then available he came to believe that it was "foam-like" in structure, meaning that it consisted of minute droplets suspended in another fluid. In other words, he thought protoplasm to be what now is termed an emulsion. He imitated this "foam-like" structure of protoplasm with emulsions prepared with olive oil, potassium carbonate, and water. Thus he obtained a water and oil emulsion of which the watery phase contained, besides potassium carbonate, also potassium soap. When he placed drops of such emulsions in water, or, better, in dilute glycerin, he found that they moved much as an amoeba moves. He noted also that the streaming phenomena in these drops were similar to those described in amoebae, in that there was an axial current in the direction of movement which spread out toward the sides at the anterior end. Currents of this nature (observed earlier by Berthold, 1886, and Quincke, 1888) arise when the surface tension of a drop is locally lowered, as happens when one side of a drop of oil in water is touched by a soap solution (Fig. 3). The drop moves in the direction of the soap solution. Bütschli explained this movement in the following way. Some of the soap solution is swept toward the posterior end of the drop by the currents at the surface of the drop. As this material is removed, it is then replaced by the soap solution, by the water, and also by the oil. Since the oil drop tends to keep its form, the drop itself moves forward.

According to Bütschli, the movements of emulsion drops in water or in dilute glycerin can be similarly explained. The surface tension would be lowered locally by soap solution that leaves the watery phase of the emulsion by diffusion or by the bursting of superficial alveoli. As a result, currents are set up which produce the movement of the drop.

Applying these ideas to the movement of amoebae, Bütschli assumed that protoplasm was an emulsion of droplets of a watery solution in a fluid not soluble in water. This fluid he held to be identical to the plastin of Reinke and Rodewald (1881). He thought it probable that the droplets contained soap-like compounds which poured out on the surface of the amoeba with the bursting of superficial alveoli. Just as in a drop of oil emulsion, the surface tension would be locally lowered, currents would be created, and movement would occur. Bütschli believed this explanation to hold not only for simple monopodal movement (*A. limax*, *Pelomyxa*, etc.) but to be equally tenable for more complicated changes in form involving several pseudopodia.

In an appendix to his book, Bütschli reported his observations on the currents in the water around a moving *Pelomyxa*. As has been mentioned, Berthold had rejected the idea that the currents in amoebae were caused by the same factors as those in moving drops, because he could not observe currents in the water around moving amoebae such as he saw around the drops.

Bütschli did find currents around *Pelomyxa*, but they seemed to run in a direction opposite to what he expected on the basis of his experiments with drops. As a tentative explanation for this difference, he suggested that the superficial layer of the protoplasm might be more viscous than the inner mass, and that there might be a current running toward the anterior end. In other words, two currents would occur at the surface: one in the internal zone, running backward as in moving drops, and one in the external zone, running forward. Bütschli did not observe superficial forward-running currents, but they were later reported by Blochmann (1894), who agreed with Bütschli as to the forward current in the medium outside the moving amoeba. However, Blochmann's observations regarding forward currents inside amoebae have not been confirmed by other investigators, although detailed studies have been undertaken. Whether or not such currents exist, the fact remains that the currents in the medium *around* moving amoebae are different from those around moving drops. Since the nature of the currents in the medium is an essential factor in Bütschli's explanation of the forward movement, it must be concluded that his theory is not adequate.

It is interesting to note that according to Bütschli's own description the currents in moving amoebae are not entirely the same as those in the moving drops. In the drops he found that the currents under the surface continue backward and then bend toward the axial stream (Fig. 3), while in moving amoebae he observed that these currents move backward only a short distance and then come to rest. This agrees with Schulze's observations (Fig. 1). Bütschli used the similarity of these currents as his basic evidence that the mechanism of the movement of amoebae was the same as that of drops of which the surface tension is locally lowered. The fact that the identity he alleged for the currents is not in agreement with his observations further weakens his theory.

The surface tension theory was again modified by Rhumbler (1898a, b). This investigator agreed with Berthold and Bütschli that protoplasm is essentially a fluid, but he emphasized that in an amoeba the surface (ectoplasm) is more dense and more viscous than the interior (endoplasm). According to Rhumbler, the ectoplasm is of tougher consistency because of contact with the external medium. Further, he assumed that amoebae secrete a sticky substance at the place of contact with the substrate and so create the friction between the cell and the substrate necessary for progressive movement. The mechanism of amoeboid movement he described as follows (Fig. 4): For an unknown cause, which may originate in the medium or in the cell body itself, the surface tension is locally reduced at some place on the surface of the cell. As a result, the protoplasm bulges out at the point of lowered surface tension (from A to A_1), bringing about an axial current in the endoplasm. Because of the increase in surface area at the anterior end, protoplasm which previously was under the surface is now located at the surface, where contact with the external medium transforms it from endoplasm

FIG. 4. RHUMBLER'S CONCEPT OF AMOEBOID MOVEMENT

SS, sticky substance; RP, resting protoplasm; A, anterior end; P, posterior end. For explanation see text. After L. Rhumbler (1898a).

to ectoplasm. This newly formed ectoplasm attains only gradually the viscosity of the older ectoplasm, and, according to Rhumbler, the surface tension remains lower here than at other parts of the surface of the cell body, and further bulging results. Since by this bulging more new ectoplasm is formed, the ectoplasm formed earlier takes up a position relatively further back. As endoplasm streams forward in the axial current, ectoplasm at the posterior end moves forward too, becoming thicker in mass. Here the inner portion of the ectoplasm, because it is farther removed from the surrounding medium, is transformed into endoplasm. Thus, as the amoeba moves forward, endoplasm is continuously transformed to ectoplasm at the anterior end, and at the posterior end this transformation is reversed. The essential features of this so-called "ectoplasm-endoplasm process" had previously been described by Wallich (1863 a, b, c), A. Gruber (1882, 1885, 1886–87), and particularly by F. E. Schulze (1875).

According to Rhumbler's papers of 1898, he did not attach particular significance to the occurrence of "fountain currents." He believed that a true fountain current, i. e., a forward-directed current which spreads to the sides and then turns backward, did not always occur at the anterior end of a moving amoeba. If such a current occurred, he explained it rather vaguely as being caused by the transformation of endoplasm into ectoplasm at the advancing end, which would be accompanied by a change in density, which in turn would push material backward. Just exactly what the force was which directed the current backward he did not explain. His opinion differed markedly from that of previous investigators, who held that the fountain currents resulted directly from a local lowering of the surface tension, and who based their evidence for the presence of local changes in surface tension on the occurrence of fountain currents.

As a result of Jennings' observations (1904) which will be discussed in detail later, Rhumbler changed his views in 1905. After Jennings had denied the presence of any fountain currents in moving amoebae, Rhumbler emphasized their occurrence in various amoebae (*A. blattae, Pelomyxa penardi, A. proteus, A. limax*) and apparently regarded their existence in these cases as proof for the activity of surface tension forces.

For movements without typical fountain currents, Rhumbler accepted Jennings' explanation, according to which the amoeba moves forward by a rolling motion. His views regarding the forces bringing about the movement in this type of motion are about as follows. At the anterior end the forces would be the same as those which determine spreading of a drop in a liquid medium and in contact with a solid surface. This is identical with the theory earlier put forth by Berthold. However, Rhumbler believed that at the posterior end there was another force. This force he assumed to originate from a gelation process, which by means of dehydration produced contraction ("Gelatinierungsdruck"). He believed the contraction to serve the same function as the surface tension forces which constituted the moving agent in amoebae moving with fountain-currents.

Rhumbler is not quite clear regarding the relative importance of the surface tension forces at the anterior end and the contraction at the posterior end. It is obvious, however, that he believed in the existence of two different mechanisms in amoeboid movement, one of them no different in essence from the mechanisms proposed by the adherents of the earlier contractility theories. It is remarkable, however, that in a later paper (1907) he still seemed to think that the mechanism of amoeboid movement could be fully explained by the activity of surface tension forces.

The forces at the surface were somewhat more accurately analyzed by Jensen (1901, 1902). He considered these forces to consist (1) of a normal pressure (the resultant of the forces of attraction by the molecules in the fluid), and (2) of a pressure due to the curvature of the surface $\left(\frac{-2T}{R}\right)$. The sum of these forces he designated as surface pressure. A decrease of either of these two forces would result in a bulging out of the fluid, since the pressure elsewhere would remain the same. As this happened, the radius of the curvature at this place would become smaller and the pressure due to the curvature of the surface would increase. If the reduction of the pressure at the surface were not too great, an equilibrium would be established. A withdrawal of the protrusion would occur if the surface pressure increased again. Jensen so explained the formation and retraction of short blunt pseudopodia, and said that long filamentous pseudopodia would result whenever the surface pressure at the tip continued to be less than at the rest of the surface.

Jensen's analysis did not introduce a new concept of amoeboid motion. The factors determining the force, which he termed surface pressure, are essentially the same as those which determine the force to which the previous authors refer as surface tension. Moreover, his analysis insufficiently explains amoeboid movement, since he did not consider continuous progressive movement.

There have been several attempts to explain the mechanism which would bring about the changes in surface tension resulting in amoeboid movement. Most of these explanations are purely hypothetical. As mentioned before, Bütschli (1892) believed that saponaceous compounds were released from the cell and, by contact with the surface, locally reduced the surface tension. Other investigators thought that the changes in surface tension resulted from metabolic changes in the

cell. For example, Verworn (1892, 1894) associated them with the chemical activity of oxygen. He based this opinion largely on experiments by Kühne (1864), who had shown that in an oxygen-free atmosphere amoebae stopped moving and remained fixed in the amoeboid shape they had assumed during their movement.

The hypotheses advanced by Hirschfeld (1909) and McClendon (1911) were founded on the fact that the surface tension is dependent on the interfacial potential. According to Hirschfeld the CO_2 produced by the amoeba gives its proteins an electric charge, by which the amoeba is able to react with ions or other charged particles, with resultant changes in surface tension. McClendon was more specific. He believed that the permeability of the surface membranes of amoebae was greater for cations than for anions, and that therefore HCO_3^- and $CO_3^=$ ions would accumulate in the cell, while the H^+ ions would penetrate the membrane. This would cause an electric polarization of the membrane, which would vary in proportion with the CO_2 production. Local differences in CO_2 production could thus cause local differences in polarization, which in turn would result in local changes in surface tension. McClendon experimentally showed Bütschli's thesis, according to which saponaceous substances lowered the surface tension and thus produced movements, to be incorrect. By means of a fine pipet he brought a soap solution near an amoeba and found that the amoeba moved away from the soap solution instead of toward it, as would be the case if Bütschli's hypothesis were correct. McClendon explained this by assuming that the soap solution increased the permeability for anions.

Still another explanation for a mechanism to lower the surface tension was proposed by Fürth (1922). He believed that lactic acid was produced during amoeboid movement. Since lactic acid lowers the surface tension of protein suspensions, Fürth supposed that the local production of lactic acid in amoeba would similarly result in a local reduction in surface tension. He believed also that swelling of protoplasmic particles, as a result of lactic acid production, plays a role in amoeboid movement.

That surface tension forces are active in the movement and changes in form of amoebae and white blood cells was a view accepted by many other investigators, including K. Gruber (1912), Haberlandt (1919), Tait (1918–1920), and others. A discussion of their work is omitted, since their views do not differ materially from those presented above.

Criticism and Discussion of the Surface Tension Theories of Amoeboid Movement

The surface tension theories of amoeboid movement rested mainly on the assumption that protoplasm is fluid, and hence its behavior is governed by the same physical laws which determine the behavior of a liquid in contact with a solid and (or) another liquid. That protoplasm actually follows these laws was thought to be proved by the similarity of the currents in a moving amoeba to the currents in a drop set in motion by a local lowering of the surface tension.

The currents which occur in a drop moving under the influence of a locally lowered surface tension are termed "fountain currents." They are characterized by an axial current in the direction of movement, which at the anterior end flows outward toward the sides and then moves backward along the surface. At the posterior end the current bends inward to form the axial current (Fig. 3). According to Bütschli (1892), the backward current in moving amoebae comes to rest with respect to the substrate soon after it has turned backward. In this he supported F. E. Schulze's (1875) descriptions (Fig. 1). Although these observations showed that the currents in a moving amoeba are not entirely identical with those in a moving drop, Bütschli believed that they were enough alike to substantiate his theory of amoeboid movement. The difference he explained as due to the greater viscosity of protoplasm. He also stated that in drops moving very slowly, such short backward currents sometimes occur.

Rhumbler (1898a, b, 1905) and also K. Gruber (1912) believed that true fountain currents occur in moving amoebae, but only occasionally. For amoebae moving without fountain currents, Rhumbler proposed a different mechanism, in which contraction caused by gelation replaced at least partially the surface forces. However, he still seemed to believe the surface tension theory to be generally applicable (Rhumbler, 1907).

Jennings (1904) was the first to claim that the currents in a moving amoeba differ essentially from those in a drop of fluid whose surface tension

is locally lowered. On this basis he rejected the theories which explained amoeboid movement as caused by a local decrease in surface tension. This investigator made a careful analysis of the currents in *Amoeba limax*, *A. proteus*, *A. angulata*, *A. verrucosa*, and *A. sphaeronucleolus*, by studying the movements of their granules. He concluded that there is no backward marginal current; that in reality the protoplasm here is at rest. He said that the impression that such a current exists is created by contrast with the forward axial current. Jennings' account of the currents in amoebae in locomotion is as follows (Fig. 5A).

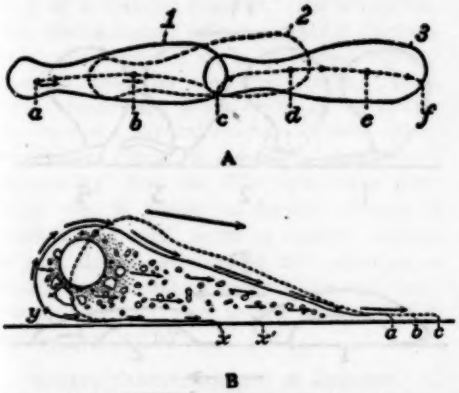


FIG. 5. A, DIAGRAM OF THE MOVEMENT OF A PARTICLE IN A MOVING AMOEBA. B, "ROLLING MOVEMENT" IN AMOEBA ACCORDING TO JENNINGS

A, As seen from above (Jennings, 1904). B, Seen in side view. For explanation see text (Jennings, 1904).

In the direction of movement there is an axial current which spreads out fanlike at the anterior end, so that some of the granules closely approach the lateral margin of the amoeba. Here the granules stop, while the central current goes on. The rest of the substance of the amoeba advances, but these granules, located at the lateral border of the cell, remain at rest with respect to objects in space. Finally the posterior end of the main body of the amoeba reaches these granules and they are then taken up in the central current, pass to the anterior end, to come again to rest. Jennings said that at no point of their course do the granules move backward with respect to the substrate.

Jennings also studied the movements at the surface of a moving amoeba. He mixed soot with the water in which the amoebae were present and observed the behavior of the soot particles which adhered to them. By this method he was able to determine that in *Amoeba verrucosa* and in *A. sphaeronucleolus* the upper surface moves forward, rolls over the advancing edge, and then comes to rest. At the posterior edge the surface moves upward and then at the upper surface again moves forward. In other words, the surface of these species of *Amoeba* rotates in the direction of movement; they progress by means of a rolling motion. It is as if a rubber sac filled with fluid were rolling over a solid support, the rubber sac representing the ectosarc and the fluid contents the endosarc.

Jennings found that at one important point the movement of such an object differs from that of an amoeba. This is best made clear with the aid of Jennings' diagram (Fig. 5B). The amoeba is attached to the substrate at its anterior end (from a to x). The upper surface moves forward as indicated by the arrows. A similar current is also present inside the amoeba. As the amoeba moves forward, the upper surface rolls over and the anterior edge moves from a to b and subsequently to c. The posterior edge of the area attached to the substrate (x) becomes free and the posterior margin is now at x^1. The material at the surface in contact with the substrate is at rest with respect to points in space. But the lower surface posterior to x and not in contact with the substrate is not at rest, as would be expected if the movement were a true rolling movement. Rather, it moves slowly forward. Jennings said this forward movement is caused by a contraction of the unattached posterior portion of the endosarc. Here not only the upper surface moves forward, but also particles on the sides and under surface. He held that this contraction does not occur in that part of the amoeba which is in contact with the substrate but begins at once when the attachment ceases.

The essential features of the movement of amoebae as described by Jennings are the same as those of drops which move as a result of one-sided adherence to a solid substrate. This seemed to strengthen the theory of amoeboid movement proposed by Berthold in 1886. However, Jennings did not believe that amoebae moved by a one-sided adherence caused by spreading on a solid substrate, for this explanation did not account for the free extension of pseudopodia into the water—the same objection which made Berthold's

theory inadequate. While Jennings concluded that surface tension forces were not responsible for the locomotion of amoebae, he did not propose a new theory and said the physical factors involved in the mechanism of amoeboid movement were as yet unknown.

It is rather curious that Jennings did not attach more significance to his observations on the contraction of the ectosarc. He did not doubt that the outer layer of *Amoeba* had the power of contraction, and he reported several observations giving evidence for this. Also, he observed that during locomotion a contraction of the protoplasm took place by which the posterior half of the cell body was pulled forward. However, he seemed to believe that this contraction played no active role in the progressive movement of amoebae, but was an inessential secondary phenomenon.

The surface tension theories were rejected also by Dellinger (1906), this time on the basis of the fact that an amoeba does not have the shape nor the behavior of a drop of fluid in contact with a solid substrate. By means of an ingenious technique Dellinger observed the movement of *Amoeba* and *Difflugia* from the side. Viewing them this way, he found that *Difflugia* moved in the following fashion (Fig. 6A). A pseudopodium is extended free in the water and becomes attached at the tip. This pseudopodium contracts and draws the shell up to the point of attachment. While this happens a new pseudopodium arises at the base of the first one and increases in length. This new pseudopodium subsequently becomes attached and then begins to contract, and the process is repeated. According to Dellinger, *Amoeba verrucosa* moves with the rolling motion described by Jennings, but other forms move in essentially the same fashion as *Difflugia*. For example, he found that in *Amoeba proteus* (Fig. 6B) the anterior end is stretched out into the medium and then becomes attached at the tip. Meanwhile, the posterior end contracts. Then a new protrusion is formed at the anterior end, which again becomes attached to the substrate, while the contraction continues at the other end.

It is obvious from Dellinger's observations that an amoeba cannot be regarded as a drop of fluid, and that the physical laws governing the behavior of fluid cannot be applied to the locomotion of amoebae, as is required by the surface tension theories. Dellinger did not make a detailed study of the protoplasmic processes involved in the mechanism of this "walking movement." He concluded that the movements of *Amoeba* and *Difflugia* are caused by a contractile substance, which is distributed through the cell as a coarse reticulum, the physical nature of which he did not define. In this respect his theory did not differ from the earlier contractility theories.

Hyman (1917) confirmed Dellingers's observations and brought forward further evidence that amoeboid organisms have properties which indicate that their protoplasm is not in a fluid state.

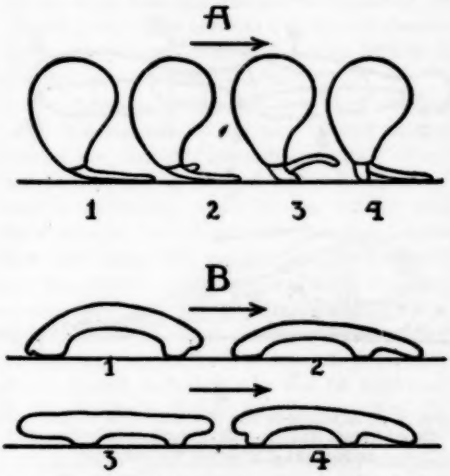


FIG. 6. "WALKING MOVEMENT" IN DIFFLUGIA SPIRALIS (A) AND IN AMOEBA PROTEUS (B), AS SEEN IN SIDE VIEW

For explanation see text. After O. P. Dellinger (1906).

As a result, this investigator also decided that considerations regarding the surface tension at liquid interfaces are not applicable to amoeboid movement. The theory she did evolve is presented in the following section on sol-gel changes.

That the surface tension theory could not explain the movement of the pseudopodia of amoebae feeding on paramecia was demonstrated by Mast and Root (1916). They observed that the pseudopodia of *Amoeba* could develop enough force to cut paramecia in half. When they calculated how much force was needed to cut through a paramecium, they found that the necessary reduction in surface tension would exceed by many times the surface tension of protoplasm.

Beers (1924) came to the same conclusion regarding *Amoeba* feeding on *Frontonia*.

However, the surface tension theories of amoeboid movement were well entrenched. Although the criticism of them was well founded, they were not immediately abandoned. Even after their primary postulate—that protoplasm was a fluid and behaved physically as a fluid—was proved incorrect, they were relinquished only reluctantly. The endurance of the surface tension theories in the face of observations indicating their inadequacy perhaps is explained by the desire to interpret vital phenomena in terms of simple physical or chemical processes. The surface tension theories seemed to have a physical exactness which was lacking in the early contractility theories, in which the term "contractility" stood for a phenomenon which could not be further analyzed on a physical or chemical basis. However, in this respect the expression "protoplasmic contractility" does not differ from many other terms used in biology to describe concepts of which the physical nature is obscure. As will be seen, the present views on the mechanism of amoeboid movement are closer to the early contractility theories than to the surface tension theories proposed later.

SOL-GEL TRANSFORMATIONS IN AMOEBOID MOVEMENT

At the beginning of this century, colloidal concepts began to be applied to the study of protoplasm. The recognition that protoplasm was a colloid not only provided a suitable terminology to describe the state of protoplasm but also gave a better insight into some of its properties. The study of the mechanism of amoeboid movement profited greatly from this development, and an accurate description of the protoplasmic processes, based on definite physical concepts, became possible.

Hyman (1917) was one of the first investigators to refer to differences in the consistency of the protoplasm of *Amoeba* in distinct colloid chemical terms. She pointed out that the ectoplasm has the properties of a gel whose degree of rigidity varies in the different species; she considered the endoplasm to be a sol of a varying viscosity. She explained amoeboid movement in the following way. Local metabolic changes in the superficial gel layer cause a solation. Because of the tension exerted by the ectoplasmic gel, the endoplasm flows out at this point, forming a pseudopodium. As the pseudopodium so formed comes in contact with the water, its surface gelates again; the metabolic change causing the solation is continuous in order to explain the continuous production of a pseudopodium. The tension of the ectoplasm which forces the pseudopodium forward is, according to Hyman, nothing else than the elastic tension characteristic of a colloidal gel.

In Hyman's view, the withdrawal of pseudopodia is essentially a process of gelation, during which the protoplasm develops the property of contractility, which she holds to be inherent in the gelation process: "I should therefore state emphatically that the property of protoplasm, which we call contractility, is nothing more or less than the gelation of an emulsoid colloidal solution; or, as we like to say in science, gelation is the 'cause' of contractility."

From this it may be concluded that Hyman believes that two forces are active in amoeboid movement: (1) a force which results from the elastic tension of ectoplasm and is active in the production of pseudopodia, and (2) a contractile force, which results from the gelation of protoplasm and which produces the withdrawal of pseudopodia. It is not quite clear whether Hyman believes this contraction to take place during the process of gelation, or after the gel is formed. If the latter, the contraction could be compared to the phenomenon of syneresis of gels. From the above quotation it appears that she thinks that a contraction accompanies the gelation process itself, but with regard to this contraction she refers to literature in which the syneretic contraction of gels is discussed. As to the force which results from the elastic tension of the ectoplasm, she does not state what force causes the stretching necessary to produce the elastic tension. Furthermore, her theory fails to account for that continuous action of either the elastic tension or the contraction which is necessary to explain progressive locomotion.

The continuity of these processes of gelation and solation involved in amoeboid movement was a particular concern of Pantin (1923), who further defined the nature of the locomotor force and the continuity of its action. Observing marine amoebae of the limax type, Pantin thought of a moving amoeba as a tube of gelated ectoplasm closed at its hind end and filled with fluid endoplasm (Fig. 7). He gave the following descrip-

tion of the processes of gelation and solation during amoeboid movement. As the endoplasm streams forward through the ectoplasmic tube, it gelates at the sides of the anterior end, thus adding to the gelated ectoplasm. In the middle the endoplasm continuously advances, because of a contraction of the ectoplasm. The endoplasmic stream originates at the closed end of the ectoplasmic tube, where solation is continuous, in pace with the gelation process at the open end. These protoplasmic processes are essentially the same as those described by Schulze, and the sol-gel changes correspond to Rhumbler's ectoplasm-endoplasm process. Pantin did not observe the "rolling movement" described by Jennings, nor Dellinger's "walking movement."

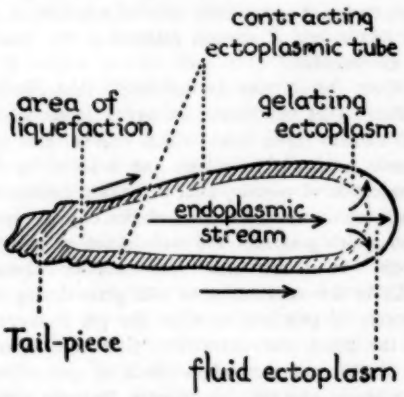


FIG. 7. SOL-GEL CHANGES IN MOVING AMOEBA
For explanation see text. After Pantin (1923).

Pantin also studied the effect on amoebae of osmotic pressure and came to certain conclusions regarding the mechanism of the contraction of the ectoplasm. He observed that in a hypertonic solution the entire amoeba came to look like the tail piece looks under normal conditions. From this he concluded that during locomotion water is abstracted from the posterior part. Because of the fluid appearance of the advancing pseudopodia, he assumed that water is here adsorbed. So, during locomotion, water would move from the posterior to the anterior part of the amoeba. By staining amoebae with neutral red, Pantin found that in an active pseudopodium there is a rise in the hydrogen ion concentration, which he believed to be the cause of the adsorption of water, resulting in swelling.

On the basis of these observations, Pantin suggested this hypothesis: A pseudopodium is extended as a result of a local acid-swelling of the protoplasm. This is accompanied by adsorption of water, which is abstracted from the posterior end. As this pseudopodium advances, a gelation process results in the forming of new ectoplasm. At the posterior end of the gelated tube of ectoplasm, water is lost by syneresis and a contraction takes place, driving forward the fluid endoplasm. During this contraction, gelated protoplasm is converted into fluid endoplasm, which is added to the endoplasmic stream. These processes result in continuous movement, since the transformation of ectoplasm into endoplasm is continuous at the posterior end, and at the anterior end the ectoplasmic tube is continuously built up by the gelation of endoplasm.

Mast (1926, 1931), who analyzed the structure of *Amoeba proteus* and the function of the different parts in locomotion, came to essentially the same conclusions as Pantin regarding solation and gelation during amoeboid movement. In addition, he described the character of the movement so as to explain the "rolling movement" observed by Jennings, as well as Dellinger's "walking movement." According to Mast, the endoplasm (plasmasol) is entirely surrounded by gelated ectoplasm (plasmagel) (Fig. 8). The amoeba is covered by a thin membrane (plasmalemma), which is separated from the plasmagel by a thin layer of fluid, except where it is in contact with the substrate. Here the plasmalemma adheres directly to the plasmagel. In Mast's theory the plasmasol is hypertonic and the plasmagel is semi-permeable and elastic, with the result that the plasmagel has an elastic tension. In locomotion, the plasmagel is locally weakened. Owing to the elastic contraction of the rest of the plasmagel, this weakened portion becomes thin and bulges out. There may be a break in the plasmagel at such a point, or the plasmagel tube may be open from the beginning (Mast, 1931). In these cases the plasmasol is in direct contact with the plasmalemma. If the advancing pseudopodium is attached to the substrate, the plasmalemma is drawn forward over the plasmagel at the upper surface, but remains stationary below; the result is a "rolling movement" of the plasmalemma. But when the pseudopodium remains free, the plasmalemma is stretched and moves forward equally on all sides, with no rolling movement.

Such a pseudopodium may become attached at the tip after it has been extended. Another pseudopodium may then be formed above it and, owing to the contraction at the posterior end of the body of the amoeba, moves over the first point of attachment. This results in "walking movement." In both cases the movement of the plasmagel and plasmasol is the same. The difference lies merely in whether the pseudopodium is attached to the substrate during its formation or becomes attached after it is formed.

As has been indicated, Mast agreed with Pantin that during locomotion plasmasol is changed into plasmagel at the anterior end and that a reverse change occurs at the opposite end. That is, the plasmagel tube at the anterior end is built up just as rapidly as it contracts and liquifies at the posterior end. The important point of difference between Mast's and Pantin's theory is in their concept of the nature of the locomotor force. For Pantin, the contraction of the plasmagel is the result of syneresis; Mast holds the plasmagel contraction to be a result of elastic recoil.

The movement of leukocytes in tissue cultures was studied by W. H. Lewis (1931, 1939, 1942), who found their manner of movement to be essentially like that of *Amoeba*, as described by Mast and Pantin. However, Lewis' concept of the locomotor force differs from that proposed by either Pantin or Mast. Lewis employed the time-lapse photomicrography technique for his studies. By projecting the film on paper and making tracings of the outlines of the cells at closely spaced intervals, he obtained accurate records of their changes in form during locomotion. As a leukocyte advances, a rigid mass of protoplasm drags behind the cell body so that the cell in motion resembles in outline the shape of a handmirror. A broad pseudopodium is present at the anterior end.

Lewis observed that when a leukocyte moves, a constriction develops at the point where the pseudopodium joins the cell body. This constriction remains stationary with regard to objects outside the cell while the leukocyte moves forward. During locomotion a succession of such "constriction rings" appears at regular intervals. Lewis assumed that the protoplasm composing the "constriction ring" remains there until the tail is reached. Thus all the protoplasm posterior to the ring, with the exception of the part composing the tail, must pass through the ring. As the "constriction ring" reaches the tail, the tail increases in length; between constriction rings, the tail shortens again. This explanation of the constriction rings is based on the assumption that white blood cells, like amoebae, have a superficial plasmagel layer, which has a contractile tension varying with its thickness or density. A local increase in thickness of the super-

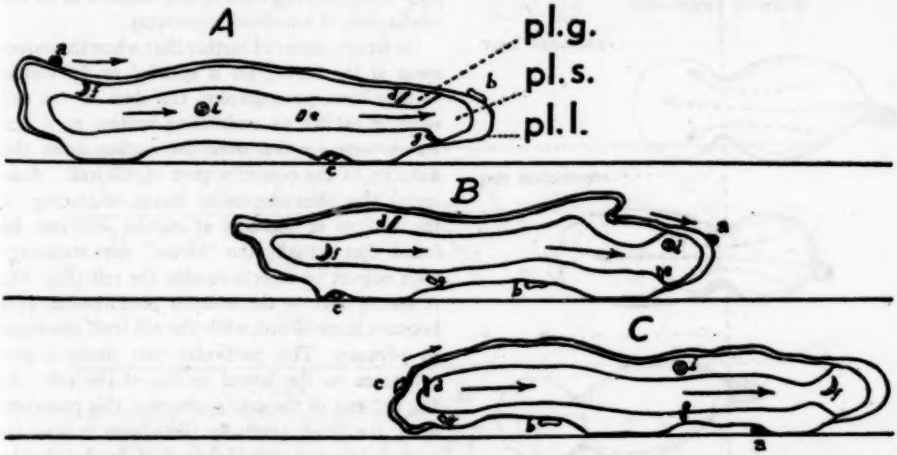


FIG. 8. DIAGRAM OF THE MOVEMENTS OF THE DIFFERENT PARTS OF AMOEBA DURING LOCOMOTION

a, b, c, particles attached to the plasmalemma (pl. l.). d, e, f, g, i, particles in plasmagel (pl. g.) and plasmasol (pl. s). (S. O. Mast, 1926).

ficial plasmagel would result in a greater contractile tension and so produce a local constriction.

Based on the above observations and assumptions, Lewis proposed an explanation for the mechanism of the locomotion of white blood cells (Fig. 9). "The contraction of the superficial plasmagel layer thrusts out a pseudopod at the weakened area and forces the endoplasm and nucleus forward through the constriction ring which does not move forward. As the plasmagel layer posterior to the constriction ring contracts, it becomes reduced in extent, gradually goes into solution until finally nothing remains but the constriction ring which then contracts down and

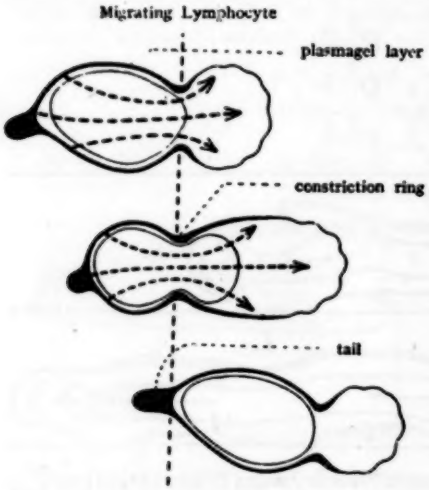


FIG. 9. LYMPHOCYTE MOVING WITH CONSTRICTION RING

For explanation see text (Lewis, 1939).

increases the length of the somewhat shortened gelated tail. The distortion of the nucleus indicates that the constriction ring exerts considerable tension. The decrease in the size of the tail in the second position indicates that some of it has gone into solution. Anterior to the constriction ring a new plasmagel layer is built up by progressive gelation at the surface from the ring inward. As the cell moves forward new constriction rings appear and the same process is repeated over and over."

As indicated above, the only difference between Lewis' hypothesis and the theories of Pantin and Mast is in Lewis' explanation of the locomotor force. Lewis regards the contractile tension exerted by the plasmagel as intimately associated with the process of gelation. "My idea is that protoplasm, like most colloids, automatically exerts contractile tension when it gels."

The investigations of De Bruyn (1946) on the movement of white blood cells in tissue cultures produced different results. Using essentially the same technique employed by Lewis, De Bruyn found that when two or more cells followed precisely the same path in the culture, they had constriction rings at precisely the same places. This indicates that constriction rings are caused by external factors and so cannot play an essential role in the locomotion of leukocytes; neither can they constitute the basis of any theories as to the mechanism of amoeboid movement.

De Bruyn observed further that when the movement of the leukocytes is speeded up by means of time-lapse photography, the sides of the cell seem to exhibit an undulating motion as if fine waves were passing over the surface from the anterior to the posterior part of the cell. Analyzing this phenomenon by means of tracings of the outlines of the cells at regular intervals, he found that actually the "waves" were stationary with respect to objects outside the cell (Fig. 10). A lateral part of the anterior pseudopodial area becomes immobilized, while the cell itself continues to advance. This particular part forms a protuberance on the lateral outline of the cell. As the tail end of the cell approaches this protuberance, the latter gradually diminishes in size, its surface becomes wrinkled and it finally shrinks away completely at the point where the tail joins the cell body. Observations on the behavior of the granules in heterophil leukocytes in locomotion indicated that the granules located in such a lateral protuberance, and frequently those located along the non-protuberant lateral outline of the cell, remain stationary with regard to points outside the cell. These granules remain stationary until they are reached by the posterior part of the cell, then they begin to participate in the streaming, which is generally in a forward direction.

De Bruyn agreed with Lewis that the movement of amoebae and leukocytes is of essentially the same nature, as indicated by (1) the similarity in the shape of moving leukocytes and moving amoebae, and (2) the behavior of the lateral protuberances as well as of the granules, which shows that in moving leukocytes, as in moving

amoebae, the lateral part of the protoplasm is stationary. Since in *Amoeba* it is the plasmagel which is stationary, it can be assumed that in leukocytes there is a similar superficial plasmagel layer, which is subjected to the same gelation process at the anterior end and solation process at the posterior end as described in *Amoeba* by Mast and Pantin. Making this assumption, De Bruyn interpreted his observations as follows. In leukocytes, the highly mobile anterior pseudopodial area consists of plasmasol, while the rigid posterior part is in the gel state. During locomotion the lateral part of the anterior plasmasol gelates and becomes immobilized. As the cell progresses this part of the plasmagel remains stationary with regard to objects outside the cell. A solation process must take place in the cell body, since plasmasol is continuously available at the anterior end. Besides giving evidence for the presence of a stationary superficial gel layer, the behavior of the lateral protuberances also indicates that a process of contraction takes place in the plasmagel. This contraction of the plasmagel has been observed only locally, i. e., in the lateral protuberances, and although this would be sufficient to account for a forward driving of the plasmasol, De Bruyn holds it probable that in analogy with the plasmagel in *Amoeba*, the whole plasmagel participates in the process of contraction.

That reversible sol ⇄ gel changes play an essential role in the mechanism of amoeboid movement seems at present well established by the observations of the above-mentioned investigators on moving amoebae and leukocytes. The question arises as to what are the causal factors of these reversible sol ⇄ gel changes. Various investigators have attempted to answer this question with very different results. Hyman (1917) believes that the sol ⇄ gel changes involve a reversal in phase in the sense that in the sol state the colloidal particles are dispersed in the fluid phase, while in the gel state the fluid phase is dispersed and the colloidal material forms the continuous

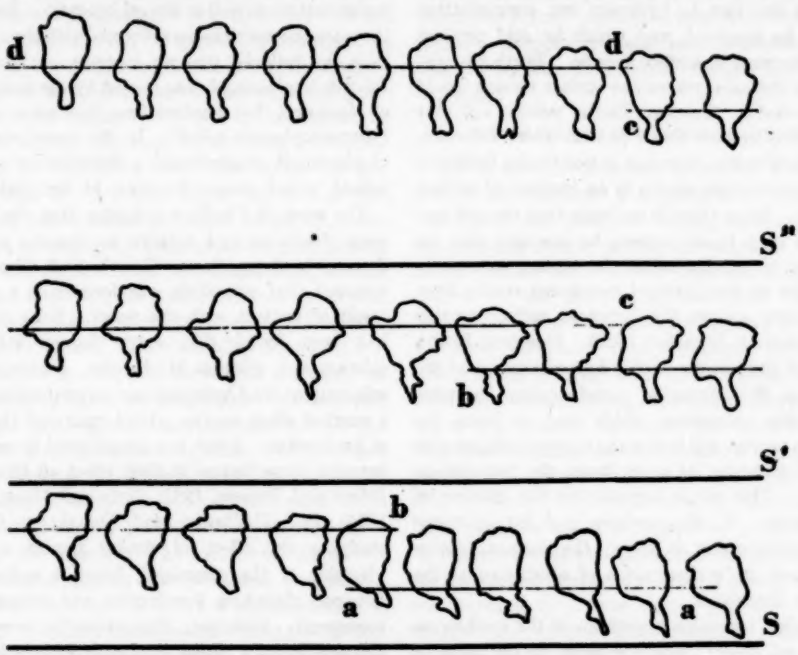


FIG. 10. OUTLINES OF A LYMPHOCYTE MOVING IN TISSUE CULTURE.

The cell moves away from S(S', S"). a–a, b–b, c–c, d–d: stationary lateral protuberances. S, S', S" are continuations of the same line. For further explanation see text. (De Bruyn, 1946.)

phase. These reversals in phase would be brought about by chemical changes originating within the amoeba. The external stimuli, which lead to the reversals in phase and thus to movement, would act via the protoplasm of the amoeba. While Hyman does not deny that an external stimulus can bring about liquefaction or gelation directly, she holds this to be improbable under the usual conditions.

Pantin (1923) related the gelation at the anterior end to the rise in hydrogen ion concentration which he observed, and which he said resulted in an increase in surface tension. Fürth thought that for the same reason the surface tension would be decreased. However, Pantin pointed out that while this is true for a protein-water interface, at a lipoid-water interface a rise in the hydrogen ion concentration results in an increase of surface tension. Since there is evidence that the cell surface is of a lipoid nature, he assumed that an increase in acidity raises the surface tension in this area so that forward movement results from work done against the increased surface tension (see also A. A. Schaeffer, 1920). However, Pantin believed that at the freshly formed surface at the sides of the advancing pseudopodium, proteins and other substances which tend to lower the surface tension will accumulate, in accordance with Gibbs' principle, so as to lower the free surface energy. This would account for the gelation of endoplasm. At the posterior end the hydrogen ion concentration is lower, the surface tension falls, and the concentration of substances at the surface diminishes.

Pantin's ingenious hypothesis of the mechanism of the sol ⇄ gel changes is based on the presence of an increased hydrogen ion concentration at the anterior end of a moving amoeba. But Mast (1926), using neutral red, was unable to find a difference in pH between the anterior and posterior parts of *Amoeba proteus*. From this he concluded that if the hydrogen ion concentration regulates solation and gelation, these processes must respond to smaller differences in pH than are detectable by neutral red; that is, any adjustment between sol ⇄ gel changes and changes in pH must be very delicate.

Chalkley (1929) believed that hydration and dehydration are involved in the transformation of plasmasol to plasmagel and the reverse. He found that changes in the gel/sol ratio and in the water content of *Amoeba* depend on the hydrogen ion concentration. The curves he obtained by plotting either the gel/sol ratio or the water content of *Amoeba* against the hydrogen ion concentration of the medium were similar to the curves obtained for the changes in hydration of an amphoteric hydrogel like gelatin under the influence of different hydrogen ion concentrations. On the basis of these observations, Chalkley postulated that there is in the protoplasm of *Amoeba* a colloid like gelatin which controls the water content as well as the gel/sol ratio. Because the water content changes directly with the gel/sol ratio, he believed that an increase of plasmagel, relative to plasmasol, was caused by the formation of plasmagel that resulted from hydration of this interprotoplasmic colloid. In the transformation of plasmagel to plasmasol a dehydration of this colloid would occur, resulting in flocculation.

The work of Chalkley indicates that the processes of solation and gelation in *Amoeba* are influenced by the medium. Even in 1905, Rhumbler assumed that ectoplasm was formed as a direct result of contact with the water. Since then it has been found that many factors influence solation and gelation in *Amoeba*. Temperature, salt content, and hydrogen ion concentration have a marked effect on the gel/sol ratio and the rate of locomotion. There is a complicated interaction between these factors in their effect on this ratio (Mast and Prosser, 1932; Pitts and Mast, 1933, 1934a, b). Heilbrunn and Daugherty (1934), studying the effect of similar factors on the viscosity of the plasmagel, found a correlation between plasmagel liquefaction and stoppage of movement. However, Mast and his coworkers did not detect a direct or specific correlation between the gel/sol ratio and the rate of locomotion.

These investigations on the influence of the above-mentioned physical and chemical factors on the gel/sol ratio do not indicate whether these factors play a role in the processes of gelation and solation as these occur in an amoeba, where they are an integral part of the mechanism of progressive movement. The relative thickness of the plasmagel and plasmasol may be only partially or not at all dependent on these processes. According to Pantin (1924), the rate of amoeboid activity is dependent on the rate at which the protoplasm can effect sol ⇄ gel changes. If this is true, then the lack of correlation between the rate of locomotion and the gel/sol ratio might indicate that the factors influencing the gelation and solation

processes at the anterior and posterior end certainly do not have a corresponding effect on the gel/sol ratio. On the other hand, Pantin's hypothesis also permits the interpretation that changes in the gel/sol ratio are caused by changes in the processes of gelation and solation at the anterior and posterior ends of the cell and thus are influenced by the same factors. The lack of correlation between the gel/sol ratio and rate of locomotion may then be explained on the basis that the factors increasing the rate of gelation do not affect equally the rate of solation, which would be necessary for an increase in the rate of locomotion. Finally, it is possible that the factors affecting the gel/sol ratio influence the rate of locomotion by another action, affecting, for example, the magnitude of the locomotive force, the absolute viscosity plasmasol, or "by their action on the surface, affecting adhesiveness and other properties of the surface, as well as by their action on permeability of the surface membrane" (Pitts and Mast, 1934b).

There is at present considerable evidence that protoplasm has thixotropic properties (Angerer, 1936; and others). The possibility that the sol ⇄ gel changes in amoeboid movement are based on this property has to be considered. The fact that amoebae in an electric current move toward the cathode, Heilbrunn and Daugherty (1939) ascribed to the thixotropic properties of the plasmagel. According to them, the protoplasmic particles in the amoeba have a positive charge and so move toward the cathode. The mechanical impact of the granules against the plasmagel produces a thixotropic solation by which a pseudopodium is formed. The fact that amoebae whose protoplasm is more alkaline move toward the anode they explain as resulting from a reversal of the charge of the protoplasmic particles.

A mechanism of the sol ⇄ gel changes during amoeboid movement based on the phenomenon of thixotropy has been proposed by Fenn (1945). He considers it possible that "the change from gel to sol during contraction is merely the result of movement which mechanically breaks up the gel, only to permit it to reform as soon as the movement ceases at the tip of the newly formed pseudopod." This hypothesis is particularly attractive, since it seems to explain the fact that there is quantitative correlation between the rate of gelation and the rate of solation in a moving amoeba. This becomes quite understandable if both processes are dependent on the same factor, i.e., on the mechanical agitation caused by the contraction of the plasmagel. In connection with this it is of interest to note that Freundlich and Soellner (1928) found that in thixotropic iron oxide sols the time necessary to set into a gel greatly depends on the pH. A similar phenomenon in the plasmasol of a moving amoeba would result in a dependence of the gel/sol ratio on the hydrogen ion concentration, without a correlation between this and the rate of locomotion. This is precisely what Mast and his coworkers found. As will be seen later, the protoplasmic changes in amoeboid movement are indeed very like the colloidal changes in a thixotropic gel.

THE NATURE OF THE LOCOMOTOR FORCE

Today most investigators agree that a contraction of the plasmagel is responsible for amoeboid movement, but there are varying opinions as to the physical nature of this contraction. W. H. Lewis (1931, 1939, 1942) says contraction is caused by the gelation process itself. Hyman (1917) also identified contraction with gelation. In connection with this hypothesis, Heyman's dilatometric investigations (1935, 1936) of the changes in volume during sol ⇄ gel transformations are of importance. He found that whether gelation is accompanied by an increase, a decrease, or by no change in volume depends on the type of sol. The thixotropic isothermal sol ⇄ gel change of an iron hydroxide sol is accompanied by no change in volume; during the setting of a methyl cellulose sol the volume increases; whereas a gelatin or agar sol decreases in volume during gelation. These changes in volume are extremely small; for example, during the setting of a 4.2 per cent gelatin sol the decrease is only 0.0026 per cent of the total volume. It seems doubtful whether such small changes could result in a contraction sufficient to produce the displacement of material seen in amoeboid movement. In addition, the work of Marsland and Brown (1936) indicates that the protoplasmic sol ⇄ gel transformation probably is not accompanied by a decrease in volume. Studying the effect of hydrostatic pressure on the protoplasm of *Amoeba dubia* and *A. proteus*, these investigators found that high hydrostatic pressures have a liquefying action on the plasmagel. From this, Marsland (1942) concluded that the protoplasmic sols are of the methyl cellulose type, which tend to increase in volume on gelation, a theory supported by the fact that gelatin sols, which

during gelation decrease in volume, gelate under pressure (Marsland and Brown, 1939). It seems, therefore, that the initial sol-gel transformation cannot of itself produce a contractile tension in the plasmagel.

An alternative interpretation of Hyman's or Lewis' hypothesis is that the tension in the plasmagel results from the decrease in volume which take place when a hydrophilic colloid dissolves or swells in a liquid. The volume reduction in such a system is considerably larger than the volume changes during sol ⇄ gel transformations (Neville and Theis, 1930). However, if such a process took place during the transformation of plasmasol into plasmagel, although there would be a contraction at the anterior end, the contraction at the posterior end, necessary to drive forward the plasmasol, could not be accounted for.

According to Mast (1926), the plasmagel is elastic and semipermeable, whereas the plasmasol is hypertonic. He said that as a consequence the plasmagel is in a state of elastic tension, and its contraction is an elastic recoil. This explanation can hold only if the plasmagel forms a closed tube system, but Mast reported later (1931) that the plasmagel tube frequently is open at the anterior end. In these cases the plasmagel can not be stretched by osmotic turgor. Since it is improbable that the mechanism of movement in amoebae with an open plasmagel tube is different from that in amoebae with a closed tube, it seems likely that an elastic recoil as a result of osmotic turgor cannot cause the contraction of the plasmagel.

Pantin (1923) believed that the contraction is caused by syneresis of the plasmagel, principally because he found evidence for an abstraction of water from the posterior part of the plasmagel. It was pointed out by De Bruyn (1946) that the sequence of protoplasmic changes in amoeboid movement shows a remarkable resemblance to the isothermal, reversible sol syneresis described by Heller(1942) in thixotropic iron oxide sols. The hypothesis that a similar process occurs in protoplasm during amoeboid movement would incorporate not only Pantin's theory but also Fenn's proposal, according to which the sol ⇄ gel changes are the result of the thixotropic properties of protoplasm. However, it is uncertain whether the physical basis of the colloidal changes in thixotropic hydroxide sols is actually the same as for the changes in protoplasm during amoeboid movement. In this connection it is of interest to note that the essential protoplasmic phenomena occurring during amoeboid movement are exhibited in vitro by plasmosin, the structural protein obtained by Bensley (1938) from the cytoplasm of liver cells. Bensley points out that the properties of plasmosin may well explain the reversible gelation of protoplasm. Plasmosin also shows a strong syneretic contraction.

Whatever the nature of the plasmagel contraction may be, the processes involved in locomotion indicate that contraction is greater at the posterior end than at the anterior end of the plasmagel and that there is a gradient in the rigidity of the plasmagel (Mast, 1926). Marsland and Brown (1936) found experimental evidence for the presence of such a gradient, and certainly a gradient would be expected if the contraction of the plasmagel is a syneretic process.

Seifriz' (1942, 1943) views are different from the ones discussed above. He believes that sol ⇄ gel changes are not an essential feature of the mechamism of amoeboid movement and says that the process of contraction is not limited to the plasmagel, but that the fluid protoplasm is equally capable of contraction. He does not elaborate his hypothesis, neither does he explain how his views account for the protoplasmic processes observed in amoeboid movement.

It is of interest to inquire whether the newer concepts of protoplasmic structure provide an adequate basis for the contraction as well as for the other processes observed in protoplasm during amoeboid movement. The prevailing concept is that the molecular structure of protoplasm is made up of a random arrangement of polypeptide chains, held together by cross-linkages of the side chains (Peters, 1937; Frey-Wyssling, 1938, 1940; Seifriz, 1942). Water, salt, carbohydrates, and fats are present in the meshes of this molecular network. According to Frey-Wyssling, side chains in varying numbers remain free. Because the side chains are never all loosened, the protoplasm is never in a true fluid state; however, as the number of loosened bonds increases, the protoplasm approaches the fluid state more closely. In streaming, the side chains would constantly be broken and reunited. Contraction can occur in such a system in two ways. First, the binding of additional side chains would cause the meshes of the three-dimensional reticulum to become narrower. Another possibility is that contraction

occurs owing to the folding of the polypeptide chains themselves (Astbury, 1939). In addition to shortening the individual polypeptide chains, this action would also narrow the meshes of the molecular reticulum, if the side linkages were maintained during the process.

In either case, contraction would be accompanied by a displacement of water, which would be taken up by previously contracted protoplasm by the reverse processes, i.e., by breaking up of side-chain linkages and/or by spring-like extension of the folded polypeptide chains. Both would produce a forward movement of the protoplasm. The process is essentially in agreement with Pantin's hypothesis, according to which water is displaced by the syneretic contraction of the plasmagel and water is absorbed at the anterior end. There is some experimental, but not conclusive, evidence that there is a differential imbibition of water in an amoeboid moving cell. When Pantin (1923) observed that a whole amoeba in hypertonic solution looks like the tail end normally looks, he concluded that during amoeboid movement water is abstracted from the tail end. De Bruyn (1946) noted that in moving leukocytes there was a wrinkling of the surface at the tail and at the lateral protuberances as they were approached by the posterior end. A similar wrinkling of the surface was observed by Mast and Doyle (1934) in amoebae, and they ascribed this appearance to a loss of water. If wrinkling of the surface in leukocytes also indicates a loss of water, it follows that the contraction of the cytoplasm during the amoeboid movement of leukocytes is accompanied by an abstraction of water.

SUMMARY

The various theories of amoeboid movement which have been proposed in the course of time have been closely related to prevailing concepts of protoplasmic structure. The early theories of amoeboid movement were based on the general protoplasmic property of contractility. To explain the physical basis of the contraction process, a contractile reticulum was postulated as the essential feature of protoplasmic structure. However, no conclusive microscopic evidence could be found for such a structure, so the early contractility theories of amoeboid movement gave way to surface tension theories. In these, amoeboid movement was seen as analogous to the behavior of a drop of fluid under the influence of a local lowering of the surface tension. The validity of these theories was questioned in turn when it was found that the currents in such drops were not entirely like the currents in an amoeboid moving cell. After it had been demonstrated that the protoplasm at the surface is not in a fluid state, making inapplicable considerations regarding the surface tension at liquid interfaces, the surface tension theories became untenable.

The introduction of colloid chemical concepts permitted for the first time an accurate description in colloidal terms of the protoplasmic processes in amoeboid movement, and the importance of reversible sol ⇄ gel changes was established.

The present theories of amoeboid movement resemble the early contractility theories in that protoplasmic contractility is again thought to be the locomotor force. The manner by which amoeboid moving cells progress has been established by observations on the movement of the different parts of the protoplasm, relative to each other and to points outside the cell. From these observations, it has been concluded that the contractility of the plasmagel is largely responsible for the movement.

To explain this process of contraction, protoplasm is conceived to be a three-dimensional network of protein chains, linked together by cross-linkages of the side chains. In such a structure contraction may occur either by a rearrangement of the side chain connections, resulting in a narrowing of the meshes of the molecular reticulum, or by a folding of the protein chain themselves.

LIST OF LITERATURE

ALTMANN, R. 1890. *Die Elementarorganismen und ihre Beziehungen zu den Zellen.* Veit & Co., Leipzig.

ANGERER, C. A. 1936. The effects of mechanical agitation on the relative viscosity of *Amoeba* protoplasm. *J. cell. comp. Physiol.*, 8: 329–345.

ASTBURY, W. T. 1939. X-ray studies of the structure of compounds of biological interest. *Ann. Rev. Biochem.*, 8: 113–132.

BARY, A. DE. 1864. *Die Mycetozoen.* W. Engelmann, Leipzig.

BEERS, C. DALE. 1924. Observations on *Amoeba* feeding on ciliate *Frontonia*. *Brit. J. exp. Biol.*, 1: 335–341.

BENSLEY, R. R. 1938. Plasmosin. The gel- and fiber-forming constituent of the protoplasm of the hepatic cell. *Anat. Rec.*, 72: 351–369.

BERNSTEIN, J. 1900. Chemotropische Bewegung eines Quecksilbertropfens. Zur Theorie der amöboiden Bewegung. *Pflügers Arch. ges. Physiol.*, 80: 628–637.

BERTHOLD, G. 1886. *Studien über Protoplasmamechanik.* A. Felix, Leipzig.

BLOCHMANN, F. 1894. Kleine Mitteilungen über Protozoen. *Biol. Centralbl.*, 14: 82–91.

BRÜCKE, E. 1861. Die Elementarorganismen. *Sitzber. kaiserl. Akad. Wiss., Math.-Naturwiss. Cl.*, 44 (II. Abt.): 381–406.

——. 1862. Das Verhalten der sogenannten Protoplasmaströme in der Brennhaaren von *Urtica urens* gegen die Schläge des Magnetelektromotors. *Sitzber. kaiserl. Akad. Wiss., Math.-Naturwiss. Cl.*, 46 (II. Abt.): 35–38.

BÜTSCHLI, O. 1892. *Untersuchungen über mikroskopische Schäume und das Protoplasma.* W. Engelmann, Leipzig.

CHALKLEY, H. W. 1929. Changes in water content in *Amoeba* in relation to changes in its protoplasmic structure. *Physiol. Zool.*, 2: 535–574.

DE BRUYN, P. P. H. 1944. Locomotion of blood cells in tissue cultures. *Anat. Rec.*, 89: 43–63.

——. 1945. The motion of the migrating cells in tissue cultures of lymph nodes. *Anat. Rec.*, 93: 295–315.

——. 1946. The amoeboid movement of the mammalian leukocyte in tissue cultures. *Anat. Rec.*, 95: 177–192.

DELLINGER, O. P. 1906. Locomotion of Amoebae and allied forms. *J. exp. Zool.*, 3: 337–358.

DUJARDIN, F. 1835. Récherches sur les organismes inférieurs. *Ann. Sci. nat. Zool.*, 4: 343–377.

——. 1838. Mémoire sur l'organisation des Infusoires. *Ann. Sci. nat. Zool.*, 10: 230–315.

ECKER, A. 1849. Zur Lehre vom Bau und Leben der contractilen Substanz der niedersten Thiere. *Z. wiss. Zool.*, 1: 218–245.

EHRENBERG, C. G. 1830. *Organisation, Systematik und geographisches Verhaltniss der Infusionsthierchen.* F. Dümmler, Berlin.

——. 1832. *Zur Erkenntniss der Organisation in der Richtung des kleinsten Raumes.* F. Dümmler, Berlin.

ENGELMANN, TH. W. 1879. Physiologie der Protoplasma- und Flimmerbewegung. *Hermann's Handb. Physiol.* 1: 343–408.

FENN, W. O. 1945. Contractility. In Höber's *Physical Chemistry of Cells and Tissues.* Blakiston, Philadelphia.

FLEMMING, W. 1882. *Zellsubstanz, Kern und Zelltheilung.* F. C. W. Vogel, Leipzig.

FREUNDLICH, H., and K. SOELLNER. 1928. Ueber die Beeinflussung der Thixotropie des Eisenoxydsols durch schwerlösliche Stoffe. *Koll. Z.*, 44: 309–313.

FREY-WYSSLING, A. 1938. *Submikroskopische Morphologie des Protoplasmas und seiner Derivate.* Borntraeger, Berlin.

——. 1940. The submicroscopic structure of the cytoplasm. *J. roy. micr. Soc.*, 60: 128–139.

FROMMANN, C. 1880. Zur Lehre von der Struktur der Zellen. *Jen. Z. Naturw.*, 14: 458–465.

FÜRTH, O. 1922. Zur Theorie der amöboiden Bewegungen. *Arch. Néerl. Physiol.*, 7: 39–45.

GREEFF, R. 1874. *Pelomyxa palustris*, ein amöbenartiger Organismus des süssen Wassers. *Arch. mikr. Anat.*, 10: 51–73.

GRUBER, A. 1882. Beitrage zur Kenntnis der Amöben. *Z. wiss. Zool.*, 36: 459–470.

——. 1885. Studien uber Amöben. *Z. wiss. Zool.*, 41: 186–225.

——. 1886–87. Die Frage nach dem Bestehen verschiedener Plasmaschichten im Weichkorper der Rhizopoden. *Biol. Zbl.*, 6: 5–8.

GRUBER, K. 1912. Biologische und experimentelle Untersuchungen an *Amoeba proteus. Arch. Protistenk.*, 25: 316–376.

HABERLANDT, L. 1919. Uber amöboide Bewegung. *Z. Biol.*, 69: 409–436.

HEILBRUNN, L. V., and K. DAUGHERTY. 1934. A further study on the action of potassium on Amoeba protoplasm. *J. cell. comp. Physiol.*, 5: 207–218.

——, and ——. 1939. The electric charge of protoplasmic colloids. *Physiol. Zool.*, 12: 1–12.

HEITZMANN, C. 1873. Untersuchungen über das Protoplasma. I. Bau des Protoplasmas. *Sitzber. kaiserl. Akad. Wiss., Math.-Naturwiss. Cl.*, 67 (III. Abth.): 100–115.

HELLER, W. 1942. Reversible aggregations of colloidal particles. III. Isothermal reversible sol syneresis. *J. phys. Chem.*, 46: 783–793.

HEYMANN, E. 1935. Studies on sol-gel transformations. I. The inverse sol-gel transformation of methylcellulose in water. *Trans. Faraday Soc.*, 31: 846–864.

——. 1936. Studies on sol-gel transformations. II. Dilatometric investigations on iron hydroxide, gelatin, methylcellulose, silicic acid and viscose. *Trans. Faraday Soc.*, 32: 462–473.

HIRSCHFELD, L. 1909. Ein Versuch einige Lebenserscheinungen der Amöben physikalisch-chemisch zu erklären. *Z. allg. Physiol.*, 9: 529–534.

HOFMEISTER, W. 1865. Ueber die Mechanik der Bewegungen des Protoplasma. *Flora*, 48: 7–12.

HYMAN, L. H. 1917. Metabolic gradients in *Amoeba* and their relation to the mechanism of amoeboid movement. *J. exp. Zool.*, 24: 55–99.

JENNINGS, H. S. 1904. Contributions to the study of the behavior of lower organisms. 6. The movements and reactions of *Amoeba. Carnegie Inst. Wash. Pub.*, 16: 129–234.

JENSEN, P. 1901. Untersuchungen über Protoplasmamechanik. *Pflüger's Arch. ges. Physiol.*, 87: 361–417.

——. 1902. Die Protoplasmabewegung. *Ergebn. Physiol.* (part 2): 1–42.

KÜHNE, W. 1864. *Untersuchungen über das Protoplasma und die Contractilität.* W. Engelmann, Leipzig.

LEWIS, W. H. 1931. Locomotion of lymphocytes. *Bull. Johns Hopkins Hosp.*, 49: 29–36.

——. 1939. The role of a superficial plasmagel layer in changes of form, locomotion and division of cells in tissue cultures. *Arch. exp. Zellforsch.*, 23: 1–7.

——. 1942. The relation of the viscosity changes of protoplasm to ameboid locomotion and cell division. In *Structure of Protoplasm*, W. Seifriz, ed. Iowa State College Press, Ames.

LEYDIG, F. 1885. *Zelle und Gewebe.* Emil Strauss, Bonn.

MARSLAND, D. A. 1942. Protoplasmic streaming in relation to gel structure in the cytoplasm. In *Structure of Protoplasm*, W. Seifriz, ed. Iowa State College Press, Ames.

——, and D. E. S. BROWN. 1936. Amoeboid movement at high hydrostatic pressure. *J. cell. comp. Physiol.*, 8: 167–178.

——, and ——. 1939. The effects of hydrostatic pressure upon gelation phenomenon in animate and inanimate systems. *Anat. Rec.*, 75: 141–142 (Supplement).

MAST, S. O. 1926. Structure, movement, locomotion and stimulation in *Amoeba*. *J. Morph.*, 41: 347–425.

——. 1931. Locomotion in *Amoeba proteus* (Leidy). *Protoplasma*, 14: 321–330.

——, and W. L. DOYLE. 1934. Ingestion of fluid by *Amoeba*. *Protoplasma*, 20: 555–560.

——, and C. L. PROSSER. 1932. Effect of temperature, salts and hydrogen-ion concentration on rupture of the plasmagel sheet, rate of locomotion and gel/sol ratio in *Amoeba proteus*. *J. cell. comp. Physiol.*, 1: 333–354.

——, and F. M. ROOT. 1916. Observations on ameba feeding on rotifers, nematodes and ciliates, and their bearing on the surface tension theory. *J. exp. Zool.*, 21: 33–49.

MCCLENDON, J. F. 1911. Ein Versuch, amöboide Bewegung als Folgeerscheinung des wechselnden elektrischen Polarisationzustandes der Plasmahaut zu erklären. *Pflüger's Arch. ges. Physiol.*, 140: 271–280.

NEVILLE, H. A., and E. R. THEIS. 1930. The measurement of hydration of gelatin and similar materials and the relation of hydration to swelling. *Coll. Symp. Annual*, 7: 41–49.

PANTIN, C. F. A. 1923. On the physiology of amoeboid movement. I. *J. Marine Biol. Ass.*, 13: 24–69.

——. 1924. On the physiology of amoeboid movement. II. *Brit. J. exp. Biol.*, 1: 519–538.

PETERS, R. A. 1937. Proteins and cell-organisation. In *Perspectives in Biochemistry*, J. Needham and D. E. Green, eds. Cambridge University Press, Cambridge.

PITTS, R. F., and S. O. MAST. 1933. The relation between inorganic salt concentration, hydrogen ion concentration and physiological processes in *Amoeba proteus*. I. Rate of locomotion, gel/sol ratio, and hydrogen ion concentration in balanced salt solutions. *J. cell. comp. Physiol.*, 3: 449–462.

——, and ——. 1934a. The relation between inorganic salt concentration, hydrogen ion concentration and physiological processes in *Amoeba proteus*. II. Rate of locomotion, gel/sol ratio, and hydrogen ion concentration in solutions of single salts. *J. cell. comp. Physiol.*, 4: 237–256.

——, and ——. 1934b. The relation between inorganic salt concentration, hydrogen ion concentration and physiological processes in *Amoeba proteus*. III. The interaction between salts (antagonism) in relation to hydrogen ion concentration and salt concentration. *J. cell. comp. Physiol.*, 4: 435–455.

QUINCKE, G. 1870. Ueber Capillaritäts-Erscheinungen an der gemeinschaftlichen Oberfläche zweier Flüssigkeiten. *Ann. Phys. Chem.*, 139: 1–89.

——. 1877. Ueber den Randwinkel und die Ausbreitung von Flüssigkeiten auf festen Körpern. *Ann. Phys. Chem.*, 2: 145–194.

——. 1888. Ueber periodische Ausbreitung an Flüssigkeitsoberflächen und dadurch hervorgerufene Bewegungserscheinungen. *Ann. Phys. Chem.*, 35: 580–642.

REINKE, J., and H. RODEWALD. 1881. Studien über das Protoplasma. I. Die chemische Zusammensetzung des Protoplasmas von *Aethalium septicum*. *Untersuch. bot. Lab. Univ. Göttingen*, 2: 1–70.

RHUMBLER, L. 1898a. Physikalische Analyse von Lebenserscheinungen der Zelle. I. Bewegung, Nahrungsaufname, Defäkation, Vacuolen-Pulsation und Gehäusebau bei lobosen Rhizopoden. *Arch. Entwmech. Org.*, 7: 103–198.

——. 1898b. Allgemeine Zellmechanik. *Ergebn. Anat. Entwgsch.*, 8: 543–625.

——. 1905. Zur Theorie der Oberflächenkräfte der Amoeben. *Z. wiss. Zool.*, 83: 1–52.

——. 1907. Review of Dellinger's paper on Locomotion of amoebae and allied forms. *Zool. Zbl.*, 14: 614–617.

SACHS, J. 1882. *Vorlesungen über Pflanzen-Physiologie.* W. Engelmann, Leipzig.

SCHAEFFER, A. A. 1920. *Ameboid movement.* Princeton University Press, Princeton.

SCHAFER, E. A. 1883. The structure of the animal cell. *Brit. med. J.*, 2: 226–229.

——. 1891. On the structure of amoeboid protoplasm, with a comparison between the nature of the contractile process in amoeboid cells and in muscular tissue, and a suggestion regarding the mechanism of ciliary action. *Proc. Roy. Soc., Lond.*, 49: 193–198.

SCHULTZE, M. 1861. Ueber Muskelkörperchen und das, was man eine Zelle zu nennen habe. *Arch. Anat.*, 1–27.

——. 1863. *Das Protoplasma der Rhizopoden und der Pflanzenzellen.* W. Engelmann, Berlin.

SCHULZE, F. E. 1875. Rhizopodenstudien IV. *Arch. mikr. Anat.*, 11: 329–353.

SEIFRIZ, W. 1942. Some physical properties of protoplasm and their bearing on structure. In *Structure of Protoplasm*, W. Seifriz, ed. Iowa State College Press, Ames.

——. 1943. Protoplasmic streaming. *Bot. Rev.*, 9: 49–123.

TAIT, J. 1918–1920. Capillary phenomena observed in blood cells: Thigmocytes, phagocytosis, amoeboid movement, differential adhesiveness of corpuscles, emigration of leucocytes. *Quart. J. exp. Physiol.*, 12: 1–33.

VERWORN, M. 1892. *Die Bewegung der lebendigen Substanz.* G. Fischer, Jena.

——. 1894. *Allgemeine Physiologie.* G. Fischer, Jena.

WALLICH, G. C. 1863a. Further observations on an undescribed indigenous *Amoeba*, with notices on remarkable forms of *Actinophrys* and *Difflugia*. *Ann. Mag. Nat. Hist.*, 11 (3rd ser): 365–371.

——. 1863b. On the value of distinctive characters in *Amoeba*. *Ann. Mag. Nat. Hist.*, 12 (3rd ser.): 111–151.

——. 1863c. Further observations on the distinctive characters and reproductive phenomena of the Amoeban Rhizopods. *Ann. Mag. Nat. Hist.*, 12 (3rd ser.): 329–337.

THE MECHANISM OF INHIBITION OF CELLULAR ACTIVITY BY NARCOTICS

By WILLIAM D. McELROY

Dept. of Biology, Johns Hopkins University, Baltimore

INTRODUCTION

THE phenomena of enzyme inhibition have led many pharmacologists, toxicologists, biochemists, physiologists, bacteriologists, and histologists to the belief that most if not all drugs exert their effect by combining with some particular cellular protein, of which enzyme-proteins are specific examples (Clark, 1937; Bernheim, 1942; Green, 1946). The orderly and controlled physiological system which results from the integration of various enzyme catalyzed reactions has been the basis for a rational approach to the synthesis and study of specific metabolic antagonists (Woods, 1940; Fildes, 1940, 1941; Welch, 1945; Roblin, 1946). Although the fundamental mechanism of inhibition of cellular activity may be due to the combination of an inhibitor with a particular enzyme, it is difficult at times to explain the results *in vivo* on the basis of studies made *in vitro*. The narcotics, for example, have been described as relatively non-specific in their action on various enzyme systems; yet studies *in vivo* indicate that particular functions are highly sensitive to a variety of these agents. Narcosis, therefore, is usually understood to mean a temporary and reversible inhibition of some physiological response of a living system, with relatively little effect upon other processes.

Since numerous agents are known to produce a state of narcosis, it appears difficult, if not impossible, to propose a single all-inclusive theory which will account for the observed facts. In some cases chemical reactivity predominates in producing the effect, while in other cases physical properties are the important factors. Since the generally accepted narcotics include a large variety of structural types, such as the hydrocarbons, alcohols, ethers, urethanes, etc., it is evident that their common characteristic of inducing narcosis must depend upon certain physicochemical properties which they have in common. Several of these properties have been considered in previous theories of narcosis, and various reviews and books have elaborated upon them (Overton, 1901; Verworn, 1911; Warburg, 1914; Lillie, 1916; Winterstein, 1926; Meyer, 1927; Henderson, 1930; Bancroft and Richter, 1931; Clark, 1933, 1937; Cone, Forman, and Krantz, 1941; Fisher, 1942; Höber, 1945). Since the classical types of narcotics (organic non-electrolytes) appear to act in heterogeneous systems of cells and tissues either by adsorption at phase boundaries or by distribution in the lipoid phases, it is evident that application of studies *in vitro* to tissues and cells becomes difficult. This difficulty is further emphasized by the information from various studies dealing with cell structure and organization (Freundlich, 1937; Korr, 1939; Claude, 1941; Commoner, 1942; Tyler, 1942; Lazarow, 1943; Stern, 1943; Steinbach and Moog, 1945). It is generally agreed that the bulk of living matter is in the colloidal state, a large fraction being present in the form of dispersions or still more highly organized films, membranes, and fibers. All of these factors may greatly influence not only the direction but also the rate of chemical reaction. A great deal of the available information concerning the state of matter at these interfaces has come from a study of the action of homologous series of chemical compounds, among which are included many of the typical narcotics. Numerous studies of cell permeability and surface chemistry have indicated the importance of molecular orientation at these interfaces (Moulton, 1939; Adam, 1941; Bradbury and Jordan, 1942; Davson and Danielli, 1943; Rideal, 1945). The fact that molecules at interfaces are regularly oriented implies that certain peculiarities may be evident when chemical reactions take place between reactants in a film and those distributed at interfaces in the bulk phase. It may be expected, therefore, that an analysis of the mechanism of inhibition of a particular cellular process will be greatly influenced by these factors. The orientation of moleculars at interfaces offers an explanation of the observations of both Overton and Traube on the relation of lipoid solubility and surface activity to narcotic potency but does not in itself designate a mechanism of action. However, for several reasons it can be supposed that those factors which determine accumulation or orientation at interfaces are also concerned with the actual mechanism of inhibitory action.

The present review is concerned primarily with

the literature dealing with the mechanism of narcotic action *in vivo*. An attempt will be made to analyse the action of the narcotics and related compounds on cellular processes in terms of tissue-enzyme chemistry. Although it will be necessary to consider briefly the possible mechanisms of enzyme inhibition, it will not be possible or feasible to review all of the important literature dealing with this subject. The reader will be referred to other reviews which cover particular aspects of this rapidly growing field.

MECHANISM OF ENZYME INHIBITION

Several excellent attempts have been made in the past few years to determine the nature or mechanism of inhibitor action *in vivo*, and it may be expected that these methods will be of value in future studies. Even though it is to be expected that compounds will vary as to the mechanisms whereby they inhibit different systems, it is useful from a comparative standpoint to know these mechanisms both for cellular processes and for isolated enzyme systems. As we shall see later, this information will be of great value for the purpose of interpreting cellular response. As to the actual mechanism of action, as well as the site of action, inhibitors may be generally classified as competitive or non-competitive. The classification of an inhibitor is an important initial step in determining its fundamental mechanism. Various categories of competitive and non-competitive inhibitors have been recognized, and from the schematic representation of enzyme action shown in Fig. 1 the following types may be enumerated.

I. Competitive Inhibitors

A. Dependence upon Substrate Concentration

Various compounds, especially those which are similar in structure to the normal substrate molecule, may compete with the latter for the "active centers" on the enzyme. The combination of the inhibitor with the active centers prevents the formation of the enzyme-substrate complex, and therefore reduces total catalytic activity. The degree of inhibition depends upon the relative concentrations of the substrate and inhibitor molecules, as well as on the affinity of the enzyme for these two compounds. A well-known example of this type of inhibition is that in which malonic acid inhibits succinic dehydrogenase in the reaction: succinate ⇄ fumarate. Both malonic and succinic acid compete for the "active surface" on the enzyme, but only succinic acid is oxidized; malonic acid forms an inactive complex with the enzyme. Other examples of "substrate competitive inhibition" may be found in the literature (Lineweaver and Burk, 1934; Welch, 1945; Roblin, 1946).

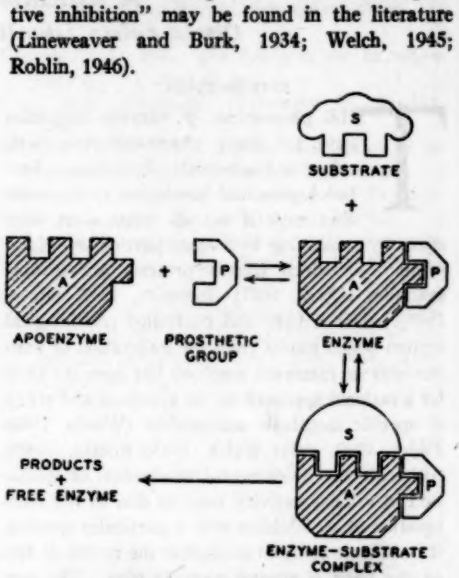


FIG. 1. A SCHEMATIC REPRESENTATION OF A HYPOTHETICAL ENZYME SYSTEM

The above scheme attempts to demonstrate the manner of combination of substrate and prosthetic group with the protein portion of the molecule. The specificity of catalytic activity of enzymes is apparently due to the surface configuration of the protein which is complementary to the substrate molecule. The actual combination of the enzyme and the substrate apparently places the latter molecule under a strain which allows for a more rapid reaction. The change in shape of the substrate molecule is used to indicate this strained condition. Various inhibitors or antagonists may compete with the prosthetic group or with the substrate for the respective centers on the protein molecule and consequently reduce catalytic activity. Other potential sites of inhibitor action are discussed in the text.

B. Dependence upon Prosthetic Group Concentration

The inhibitor and the prosthetic group may compete for the apoenzyme, the protein portion of the enzyme. In this case, the degree of inhibition will depend upon the relative concentrations of the competing compounds and the relative affinity of the apoenzyme for them. The inhibition of cytochrome c reductase by atabrine, and the reversal of this inhibition by riboflavin phosphate, is a case in point (Haas, 1944). The latter compound is

the normal prosthetic group of the enzyme, and atabrine apparently competes with it for the apoenzyme according to the reaction shown in Fig. 1. Hellerman, Lindsay, and Bovarnick (1946) demonstrated that *d*-amino acid oxidase was inhibited by atabrine in a similar manner. It is to be expected that many compounds will be found to inhibit cellular reactions in this manner. Numerous metabolic antagonists which are derivatives of growth factors, such as the vitamins, probably inhibit particular systems by such a competitive mechanism. It is important, however, to point out that a "prosthetic group competitive inhibitor" in one system may be a "substrate competitive inhibitor" or a non-competitive inhibitor in another system. Atabrine, for example, inhibits glucose-6-phosphate dehydrogenase also, by combining with the protein moiety of the enzyme. Addition of substrate reverses this inhibition, thus demonstrating a competition between the drug and the substrate (Haas, 1944).

C. Apparent Competitive Inhibition

In an isolated system containing only known components whose concentration can be controlled, it is relatively easy to determine whether inhibition is competitive with respect to substrate or prosthetic group. In cells and tissues, however, the actual substrate or the prosthetic group of the enzyme in the inhibited reaction may not be known. In this case the observed competition between two substances may be misleading. This is especially true in experiments of long duration, such as those involving growth inhibition. In the latter case the possibility of interference with the synthesis of a particular essential metabolite must be considered. Usually growth antagonists have been considered as interfering with either the "synthesis or the utilization" of a metabolite (Gaddum, 1943; Roblin, 1946). For example, when synthesis is affected, the minimum concentration of the metabolite which prevents the action of the antagonist is effective against any reasonable concentration of the latter. On the other hand, if utilization is affected, a more or less constant ratio usually persists between antagonist and metabolite over a wide concentration range (i.e., a truly competitive reaction). For classifying inhibitors on the basis of interference either with synthesis or utilization of a metabolite, the above criteria are of questionable value. This is especially true where the nature of the inhibited reaction is not known. False conclusions may result when such criteria are used to assign a definite metabolic function to substances that will reverse the action of growth antagonists. The following considerations will make this clear. If a series of reactions is involved in the synthesis of an essential metabolite, *D*, as follows:

$$A \rightarrow B \rightarrow C \rightarrow D,$$

then inhibition of the utilization of any of these precursors would interfere with the synthesis. If the conversion of *A* to *B* is blocked by any mechanism, it is possible to reverse the inhibition by the addition of either *B*, *C*, or *D*, assuming for the moment that no side reactions are involved. If *B*, *C*, or *D* can be added in sufficient quantity to meet the requirements of his case, then that concentration of metabolite will antagonize any reasonable concentration of inhibitor. If some other process depends upon the completion of the step inhibited, then an immediate physiological effect will be observed; and it is the study of this process which will yield the fundamental mechanism of action. Even an inhibition of utilization of *D* may interfere with the synthesis of some other metabolite, and in this case antagonism could again be affected as observed above. Thus in all cases inhibition may be considered to affect the utilization of a metabolite, and the nature of the antagonism by added substances merely serves to indicate the possible site of action. If the observed degree of inhibition does not change when the ratio between metabolite and antagonist is varied (by supplying *B*, *C*, or *D* in the above reaction) this may indicate that the effect is not one upon the utilization of these metabolites but rather one upon the utilization of some precursor. The inhibition of a reaction, therefore, by a specific metabolic antagonist may be expected in some cases to yield information similar to that obtained from genetic blocks (Beadle, 1945). Even if a constant ratio of metabolite to antagonist is maintained over a wide concentration range, this does not necessarily mean that the inhibition observed is a competitive one like those discussed above in *A* and *B*. Such an antagonism can be obtained by actual combination of the inhibitor with metabolite (or with other compounds) to form an inactive complex (see II A below). A detailed account of the possible ways of reversing the action of an inhibitor has been discussed elsewhere (Henry, 1943; Johnson, Eyring, and Kearns, 1943).

II. Non-Competitive Inhibitors

Those compounds which inhibit a reaction independently of substrate or prosthetic group concentration may be classified as non-competitive inhibitors.

A. Inhibitions of Activity of the Prosthetic group

The activity of the prosthetic group may be reduced in one of several different fashions. Substances like H_2S, HCN, CO, and azide will inactivate the iron-porphyrin enzymes (i.e., the cytochromes) by combining with them. Enzymes requiring calcium for their activity may be inhibited by substances, such as oxalate, which combine with calcium. Some inhibitors may combine with the prosthetic group only under definite conditions. Winzler (1943), for example, demonstrated that azide combined only with the oxidized form of the Atmungsferment and not with the reduced form. Other inhibitors may be found that will combine only with the enzyme-substrate complex or only with the enzyme-prosthetic group complex, and not with the free enzyme. Various components of enzymes (flavins, pyridine-nucleotides, thiamine, etc.) require certain functional groups. A compound interfering with or destroying such a group would reduce the catalytic activity of the enzyme. The deamination or dephosphorylation of adenylic acid is a typical example of such an inhibition.

B. Inhibition of the Apoenzyme

Since the protein portion of an enzyme depends upon certain functional groups for its activity and specificity, it is to be expected that numerous compounds will be found that will reduce catalytic activity by destroying or combining with these reactive centers. Singer (1945) has recently discussed this particular aspect of inhibitory action, and the reader is referred to his paper for references and further details.

The inhibitory action of heavy metals (Hg, Ag, Cu), trivalent organic arsenoxides, *p*-chloromercuribenzoate, iodoacetate, and bromoacetate has been attributed to their power of combining with the sulfhydryl (SH) groups of apoenzymes. Enzymes requiring intact SH groups for full activity are inhibited by these agents. For this reason, the heavy metals have been used to detect the presence of "active SH" groups in enzymes. Singer has tabulated the various enzymes which require SH groups for activity, and it is interesting to note that enzymes which perform the same function may have markedly different properties, with respect to their need for SH groups, when isolated from different sources. There are numerous other compounds, such as the quinones, which will inhibit the sulfhydryl enzymes, and many natural products are considered to inhibit enzyme action by combining with SH groups.

In addition to the SH group, others, such as $-NH_2$, phenolic OH, SS—, etc., may be essential, depending upon the amino acid composition of the apoenzyme. Various reagents that will combine with these groups can inhibit the enzymes which carry them as a functional part of their structure. As the mode of action of many of these inhibitors is elucidated, it may be expected that some will become classified as "competitive," for, as Singer has pointed out, there are several experiments which demonstrate that sulfhydryl enzymes may be protected from inhibition by the presence of a substrate. Hopkins and Morgan, for example, demonstrated that succinic acid and other dicarboxylic acids which act as competitors for succinic dehydrogenase are able to protect the enzyme against the SH reagent disulfide glutathione (see Ames and Elvehjem, 1944). These findings, along with others, indicate that the active centers on the enzyme, where the combination of substrate and enzyme occurs, contain SH groups. Thus it may not be surprising that there are highly specific inhibitors which will combine with the active centers of enzymes. The strength of this combination may depend not alone upon the active group, but also on the structural configuration of the enzyme surface at which the substrate combines. It is well known that the ability of SH inhibitors to combine with proteins containing SH groups will vary considerably, depending upon the relationship of the SH groups to the remaining groups of the protein. Some SH groups are reactive to certain reagents only after partial denaturation of the protein (Neurath, Greenstein, Putnam, and Erickson, 1944). In this respect it is interesting that the presence of substrate has a very pronounced influence upon the temperature inactivation of enzymes. It might be expected, therefore, that various inhibitors that combine with the active groups of enzymes will influence their denaturation.

KINETIC ANALYSIS OF COMPETITIVE AND NON-COMPETITIVE INHIBITION

Lineweaver and Burk (1934) have reviewed the kinetics of enzyme action, assuming the formation of an enzyme-substrate complex, and have pre-

sented equations for testing various types of inhibition. Recent important modifications of this treatment have been presented by Winzler (1943), Ebersole, Guttentag and Wilson (1944), Straus and Goldstein (1943), and Goldstein (1944).

The Michaelis-Menton treatment of enzyme kinetics is based upon the assumption that, at low enzyme concentrations, the reactions proceed according to the laws governing first order reactions. This theory was extended by Briggs and Haldane. In it the combination of the enzyme (E) and substrate (S) is represented as a bimolecular reaction. The resulting intermediate (ES) decomposes according to a monomolecular reaction into free enzyme and products (P).

$$E + S \underset{k_3}{\overset{k_1}{\rightleftarrows}} ES \qquad (1)$$

$$ES \xrightarrow{k_2} E + P \qquad (2)$$

Therefore, the breakdown of substrate (S) will proceed at velocity (V) as expressed in the following equation:

$$V = k_2 [ES], \qquad (3)$$

in which k_2 is the velocity constant of reaction 2. The concentration of the complex ES cannot be measured directly; but we may obtain the following expression for it from reaction 1:

$$[ES] = \frac{[E][S]}{K_s + [S]},$$

in which K_s is the equilibrium constant. Substituting this value of ES into equation (3) we obtain:

$$V = \frac{k_2[E][S]}{K_s + [S]} \qquad (4)$$

In the presence of a large excess of substrate virtually all the free enzyme will combine with it to form the complex, so that $[ES]$ will approximately equal $[E]$. Under these circumstances no further increase in velocity will be obtained with an increase in concentration of substrate, since no more ES can be formed; therefore, maximum velocity $(Vm) = k_2[E]$. By substituting in equation (4) we obtain the familiar velocity equation:

$$V = \frac{Vm[S]}{K_s + [S]} \qquad (5)$$

A more useful form of this equation is obtained by taking the reciprocal of both sides, since this results in a linear relation.

$$\frac{1}{V} = \frac{1}{Vm} + \left(\frac{K_s}{Vm}\right)\frac{1}{[S]} \qquad (6)$$

Multiplying equation (6) through by (S) gives an alternative form:

$$\frac{[S]}{V} = \frac{[S]}{Vm} + \frac{K_s}{Vm} \qquad (7)$$

If the reciprocal of the velocity, $\frac{1}{V}$, is plotted against the reciprocal of the substrate concentration, $\frac{1}{[S]}$, a straight line should result whose slope $\left(\frac{K_s}{Vm}\right)$ divided by the intercept $\left(\frac{1}{Vm}\right)$ equals K_s, the dissociation constant of the enzyme substrate complex.

I. Competitive Inhibitors

If an inhibitor is present an additional reaction will occur:

$$E + I \underset{k_3}{\overset{k_1}{\rightleftarrows}} EI \text{ (Inactive)} \qquad (8)$$

If the inhibitor combines at the same point on the enzyme as the substrate, then the inhibition will depend upon both the concentration of the substrate and the concentration of the inhibitor (i.e., competitive inhibition):

In this case the reciprocal of the velocity equation is

$$\frac{1}{V_i} = \frac{1}{Vm} + \frac{1}{Vm}\left[1 + \frac{[I]}{K_i}\right]\frac{K_s}{[S]} \qquad (9)$$

where V_i is the velocity at the substrate concentration $[S]$ and inhibitor concentration $[I]$. K_i is the dissociation constant of reaction (8). Thus for a competitive inhibition, the plot of $\frac{1}{V_i}$ against $\frac{1}{[S]}$ will give diverging lines with a common intercept for various concentrations of inhibitor. Thus maximum velocity does not change, but the slopes will increase by the factor $\left(1 + \frac{[I]}{K_i}\right)$. The apparent K_s = slope/intercept increases, therefore, by the same factor. An alternate method of plotting is given by Ebersole et al. (1944), in which $\frac{V}{V_i}$ is plotted against $[I]$ for several substrate concentrations. If the inhibition is competitive, straight lines are formed with unit intercept but different slopes; if non-competitive, the slopes will coincide.

As discussed previously, the direct way of demonstrating competitive inhibition is to prove that with a large amount of substrate present more inhibitor is needed to produce a given degree of inhibition than when the substrate concentration is small, or best, by following the time course of entrance of substrate or inhibitor into the reaction (Goldstein, 1944). Chance (1943) has been able to perform the latter by studying the effect of cyanide on peroxidase activity, using the Hartridge-Roughton flow method.

II. Non-Competitive Inhibition

In strictly non-competitive inhibition the combination of inhibitor with enzyme is independent of the presence of the substrate, i.e., inhibitor combines with both E and ES. In this case the reciprocal of the velocity equation is

$$\frac{1}{V_i} = \left[1 + \frac{I}{K_i}\right]\left[\frac{1}{Vm} + \left(\frac{K_s}{Vm}\right)\frac{1}{[S]}\right] \quad (10)$$

Thus in a plot of $\frac{1}{V_i}$ against $\frac{1}{[S]}$, both slope and intercept are increased by the same quantity, $\left(1 + \frac{[I]}{K_i}\right)$, so that K_s remains constant. Thus Vm is changed in the presence of a non-competitive inhibitor.

Certain variations of the behavior of competitive and non-competitive inhibitors may be expected, as was pointed out earlier. Ebersole et al. (1944) have presented the velocity equation for the type of inhibitor which combines only with ES. The inhibition in this case depends upon substrate concentration, but not in the usual competitive way. The reciprocal of the velocity equation is

$$\frac{1}{V_i} = \left[1 + \frac{[I]}{K_i}\right]\left(\frac{1}{Vm}\right) + \left(\frac{K_s}{Vm}\right)\left(\frac{1}{[S]}\right) \quad (11)$$

In a plot of $\frac{1}{V_i}$ against $\frac{1}{[S]}$ for this type of inhibition, the slope will not change, but the intercept will increase by the factor $\left(1 + \frac{[I]}{K_i}\right)$, i.e., Vm changes and the apparent K_s decreases. For intermediate cases, if the slope changes, but by a factor less than the intercept, there is indicated a greater affinity of the inhibitor for ES than for E. An example of this enzyme-substrate complex inhibition is the combination of azide with the oxidized form of the Atmungsferment (Winzler, 1943).

Since the Michaelis-Menten theory is based upon the assumption of a first order kinetic function, serious error may be encountered when attempts are made to apply it to true second order reactions. Straus and Goldstein (1943) and Goldstein (1944) have extended the theory to include both monomolecular and bimolecular reactions. Thus, beginning with reactions (1), (2), and (8) we can rewrite equation (3) as

$$V = k_3(E - EI) \quad (12)$$

for with an inhibitor present a fraction of the total enzyme will be in the inactive complex (EI), and the free enzyme available to combine with excess substrate will be $(E - EI) = ES$. Dividing V by Vm, we obtain:

$$\frac{V}{Vm} = \frac{k_3(E - EI)}{k_3E} = 1 - \frac{EI}{E} \quad (13)$$

Let i represent the fraction of the total enzyme that is combined with the inhibitor,

$$i = \frac{EI}{E} \quad (14)$$

Then

$$\frac{V}{Vm} = 1 - i \quad \text{or} \quad i = 1 - \frac{V}{Vm} \quad (15)$$

The fractional inhibition, i, can be found as usual and will vary between the limits of 0 and 1 as V varies from Vm to 0.

From reaction (8) we can set up the following relationship at equilibrium, if the law of mass action is followed:

$$\frac{(E - EI)(I - EI)}{(EI)} = \frac{k_2}{k_1} = K$$

Substituting the value for EI from equation (14) ($EI = iE$), and simplifying, we have

$$I = \frac{K_i}{1 - i} + iE \quad (16B)$$

This equation states that the total molar concentration of inhibitor $[I]$ is equal to the sum of two parts: (1) the concentration of combined inhibitor $[iE = EI]$ and (2) the concentration of uncombined inhibitor $\left[\frac{K_i}{1 - i}\right]$.

If the concentration of enzyme is small, so that

practically all of the inhibitor is in the free form, then equation (16B) simplifies to

$$I = \frac{K_i}{1 - i} \qquad (16A)$$

On the other hand, if the enzyme concentration is very large, nearly all the inhibitor will be combined, and equation (16B) simplifies to

$$I = iE \qquad (16C)$$

However, as Straus and Goldstein have pointed out, it is not the actual concentration of the enzyme that is important, but rather its magnitude in relation to the dissociation constant K. Thus the relationship E/K is used for "specific concentration" of enzyme and is designated as E'. Likewise I/K is the "specific concentration" of inhibitor and is designated as I'. If we divide equation (16B) by K and substitute we have:

$$I' = \frac{i}{1 - i} + iE' \qquad (17B)$$

In the instance where specific concentration of enzyme (E') is small and practically all of the inhibitor is free, (17B) becomes:

$$I' = \frac{i}{1 - i} \qquad (17A)$$

In this case the inhibition is a function of the specific concentration of inhibitor alone and is independent of enzyme concentration. For the case where E' is large and practically all the inhibitor is combined, the equation is:

$$I' = iE' \qquad (17C)$$

Here inhibition is a function of the specific concentration of inhibitor and enzyme (I'/E'). Thus the three forms of equation (17) describe the behavior of all enzyme-inhibitor systems acting according to reaction (8). According to Straus and Goldstein, these three equations represent three distinct zones of enzyme behavior, which they designate A, B, and C after the corresponding equations which describe them. Whether a particular reaction will fall in zone A, B, or C will depend upon the size of E' and consequently upon the acceptable error in the measurement of the fractional inhibition, i. If one accepts 1 per cent ($\Delta i = .01$) as the maximum error, then the approximate boundaries for the three zones can be established [see Straus and Goldstein (1943) for details] as follows: for $E' \lesssim 0.1$, the reaction is described by zone A. For $E' \gtrsim 100$, the reaction is described by zone C. For values of E' between 0.1 and 100, the full equation (17B) describes the reaction.

The kinetic analyses of enzyme reactions made by Michaelis and Menten, by Lineweaver and Burk, and by others have been based upon the assumption that the concentration of the active enzyme centers is relatively low. This is usually the case in an isolated system, where enzyme concentration is necessarily low because of the technical difficulties of low solubility and inability to measure rapid reaction rates. Since the majority of dissociation constants, K, are equal to or larger than 10^{-5} molar, it is evident, because of the above difficulties, that $E' = E/K$ will be less than 0.1, and consequently the reaction will be in zone A. It is only in this zone that the Michaelis-Menten kinetics apply.

If K is small enough, however, as is the case with certain enzyme-substrate complexes (10^{-8} to 10^{-7}), then the reaction may be expected to fall in either of zones B or C. The enzyme-inhibitor system of cholinesterase and physostigmine have dissociation constants as small as or smaller than this. For a single enzyme studied at a single concentration, K will in general be different for the various substances that form complexes with it, and E' will vary inversely with K. Thus for any two substances (substrate and inhibitor) whose dissociation constants differ with respect to a single enzyme, it is possible that the respective systems will fall in different zones. As Straus and Goldstein pointed out, there are situations where the enzyme concentration may be large, and yet rate of reaction will be measurable. This may occur in tissue slices or intact cells, where the enzymes may be highly localized in a certain region and even within a single cell. At these points of localization the enzyme concentration may be so large than kinetic analysis would indicate that the activity of the system lies in zones B or C even though the activity of the same total amount of enzyme would lie in zone A, if it were distributed throughout the total volume of the reaction mixture. From this it appears possible that if we could determine the zone behaviors of enzymes in isolated systems, it would be possible to estimate directly the enzyme concentration wherever enzyme is active in the intact cell.

To determine the zone in which a particular sys-

tem belongs, it is necessary to determine E' ($= E/R$). This may be done for enzyme-inhibitor systems after one has obtained an activity curve for different concentrations of I by modifying equation (16B). Straus and Goldstein divided the equation by i and obtained the following expression:

$$\frac{I}{i} = K \cdot \frac{1}{1-i} + E \qquad (18)$$

If I/i is now plotted against $\frac{1}{1-i}$, a straight line will be obtained whose slope is equal to K and whose intercept is equal to E. Straus and Goldstein found that for the fractional inhibition of cholinesterase by physostigmine in 22.2 per cent horse serum $K = 3.7 \times 10^{-8}$ and $E = 2.7 \times 10^{-8}$. This gave a value for $E' = 0.73$. This value of E' places this system found in horse serum in zone B ($E' = 3.29$ in undiluted serum).

Other important points appear when the zone behavior of enzymes is considered. From a physiological point of view one of the most important of these is the effect of dilution. In diluting an enzyme-inhibitor mixture, the specific enzyme concentration E' will always be changed to exactly the same degree as the specific inhibitor concentration I'; i.e., the ratio $\frac{I'}{E'}$ (or I/E) will be maintained constant. Important differences result when dilution is made in the several zones, and the reader is referred to Straus and Goldstein for the details and graphs demonstrating this effect. The following can be shown: (1) Within zone C, dilution has no effect whatever upon the fractional inhibition, i (see equation 17C). (2) Within zone A, the change in i produced by dilution is not influenced by initial or final specific enzyme concentrations, but only by the factor of dilution (see equation 17A). (3) Within zone B, the change in the fractional inhibition depends upon both the dilution factor and the initial and final E'. Straus and Goldstein have given other practical tests for determining zone behavior.

The above analysis of inhibitory action and zone behavior is applicable only to those cases of non-competitive inhibition where only one inhibitor combines with the enzyme. Straus and Goldstein demonstrated, however, that it was possible to extend their analysis to include those cases where more than one molecule of a substance combined with the enzyme. Goldstein (1944) later extended the zone behavior of enzyme-inhibitor action to include the competitive type of inhibition. The reader is referred to this important paper for the kinetic analysis. One interesting point that follows from that analysis is that competitive inhibition cannot exist in zone C and, conversely, if the inhibition is competitive, the zone must be A or B.

The importance of the type of analysis which has been presented by Straus and Goldstein (1943) and by Goldstein (1944) cannot be emphasized too greatly for the application of data obtained *in vitro* to the living system as a whole. Only when such factors as dilution, dissociation constant, enzyme concentration, etc., are considered together can gross errors be eliminated. It should be emphasized, however, that only in the special cases described by reaction (8) does the dissociation constant K, as measured above, represent its true value. Only by evaluating the effect of temperature and pressure on the activity of enzymes and inhibitors can the true equilibrium constant be obtained. This is discussed in some detail in the next section.

REACTION OF INHIBITORS WITH PROTEINS

Studies of the effects of reversible inhibitors upon enzyme systems have contributed greatly to our knowledge of enzyme kinetics. When an inhibitor competes with the substrate or prosthetic group for the active site on the apoenzyme, it presumably combines with or is adsorbed to the protein surface in much the same way as is the normal substrate. On the other hand, in non-competitive inhibition, the inhibitor may react with a group necessary for activity at a point different from that at which the substrate or prosthetic group combines. This reaction or combination may involve the breaking of important bonds in the protein molecule, with subsequent change in its size and shape. The nature of this combination of inhibitors with proteins has an important bearing upon the kinetic analysis presented in the previous section and should, if possible, be analysed more closely.

As a result of the recent studies by Johnson, Eyring, and associates on the effect of pressure, temperature, and inhibitors on biological reactions, it appears possible to determine in a general way the effect of various compounds upon proteins. The theory of these workers is based upon the assumption that enzymes normally exist in equilibrium between a catalytically active and an inactive form (Anson and Mirsky, 1934). It is this

equilibrium which determines the optimum temperature for biological reactions. The bioluminescent system has been used extensively in these studies. This luminescent reaction involves the oxidation of a specific substrate, luciferin, by molecular oxygen in the presence of a specific enzyme, luciferase. In the process one of the components becomes activated and subsequently emits light according to the laws governing monomolecular reactions (see Harvey, 1940, 1941). The light intensity, then, is a direct measure of the rate of reaction and offers, therefore, an excellent enzyme system upon which rapid measurements may be made.

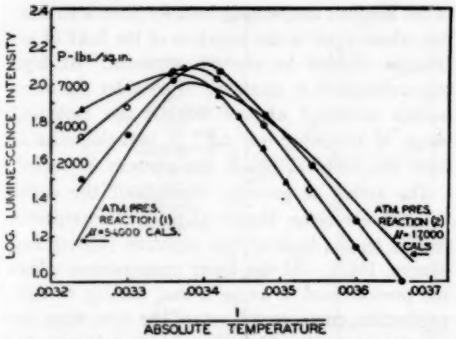
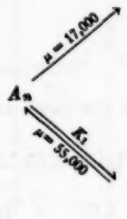


FIG. 2. THE LUMINESCENCE INTENSITY TEMPERATURE RELATION FOR PHOTOBACTERIUM PHOSPHOREUM AT VARIOUS PRESSURES

(From Brown, Johnson, and Marsland, 1942)

Using the luminescent reaction as a typical enzyme system, Johnson, Brown, and Marsland (1942a) demonstrated that the decline in light intensity above the optimum temperature may be almost entirely reversed by cooling the system, providing the high temperature is not maintained too long. This reversibility demonstrates that a thermal destruction does not take place. Because of the large heats of reaction involved in this reversible inhibition (50,000–70,000 calories), it was suggested that the reaction is a reversible denaturation of the enzyme. Known denaturation reactions possess similar temperature characteristics (Eyring and Stearn, 1939). In support of this interpretation is the effect of high pressures on the luminescent reaction at various temperatures. Pressure is known to retard any reaction that involves an increase in volume, such as occurs in the process of denaturation or in the passage of a molecule from the normal to the activated state. Therefore, pressure may be expected to have a great influence on the rate of reaction and consequently on the light intensity. Brown, Johnson, and Marsland (1942) observed, as Fig. 2 shows, that above the optimum temperature the application of high hydrostatic pressures increases the light intensity, thus supporting the above interpretation. On the basis of these and other results, the luminescence reaction has been diagrammed as follows (for reactions leading to light emission, see Harvey, 1940, 1941; Johnson and Eyring, 1944; McElroy and Ballentine, 1944):

$$A_n^* \longrightarrow A_n + h\nu \quad (19A)$$



(19B)

n which A_n is the native or active enzyme (luciferase) that becomes excited to A_n^* in an oxidative reaction and then emits light in a reaction independent of temperature. A_d is the inactive enzyme. The light intensity depends, therefore, upon the concentration of native or active luciferase which is controlled by the reversible reaction (19B) and the primary enzyme reaction (19A) leading to light emission. Thus at temperatures low with respect to the optimum, reaction (19A) predominates and (19B) is negligible. Under these circumstances we may write the following equation for light intensity:

$$I_1 = sk_2\,[LH_2][A_n] \quad (19C)$$

where

I_1 = light intensity,
k_2 = rate constant,
s = proportionality constant allowing for the units employed,
LH_2 = substrate concentration, and
A_n = active enzyme concentration.

However, at high temperatures reaction (19B) predominates, and in this case it is necessary to take into consideration the fact that the active enzyme concentration depends upon the equilibrium constant (K_1) in this reaction. If g represents the

total enzyme, active and inactive, then $g = A_a + A_d = A_a + K_1A_a = A_a(1 + K_1)$ and

$$A_a = \frac{g}{1 + K_1}$$

Under these circumstances equation (19C) becomes

$$I_1 = sk_2[LH_2]\frac{g}{1 + K_1} \tag{20}$$

According to the theory of absolute reaction rates the following expression describes the specific reaction rate, k_2 (Glasstone, Laidler, and Eyring, 1941):

$$k_2 = k_1\frac{kT}{h}K\ddagger \tag{21}$$

in which

- k_2 = specific reaction rate,
- k_1 = transmission coefficient (in most cases equal to unity),
- k = Boltzmann constant = 1.372×10^{-6} ergs per degree,
- h = Planck's constant = 6.547×10^{-27} erg-second,
- T = absolute temperature, and
- $K\ddagger$ = equilibrium constant between the activated complex and the reactants.

$\frac{kT}{h}$ is called the universal frequency factor, since it is the rate at which the activated complex decomposes once it is formed. This rate of decomposition is the same for all reactions at the same temperature. If we now substitute this value for k_2 in reaction (20) we obtain:

$$I_1 = \frac{s[LH_2]gk_1\frac{kT}{h}K\ddagger}{1 + K_1} \tag{22}$$

Since to the various equilibrium constants ($K\ddagger$ and K_1) all the principles of thermodynamics apply, we may substitute the following values for them:

$$\Delta F = -RT \ln K \text{ and } K = e^{\frac{-\Delta F}{RT}} = e^{\frac{-\Delta H}{RT}} \cdot e^{\frac{\Delta S}{R}}$$

If we assume that the substrate remains essentially constant, we may substitute and combine all constants into one. Thus equation (22) becomes:

$$I_1 = \frac{CTe^{\frac{-\Delta H\ddagger}{RT}}}{1 + e^{\frac{\Delta S}{R}} \cdot e^{\frac{-\Delta H}{RT}}} \tag{23}$$

where

- C = combined constant, as described above,
- T = absolute temperature,
- $\Delta H\ddagger$ = energy of activation,
- ΔH = heat of denaturation,
- ΔS = entropy of denaturation, and
- R = gas constant.

Equation (23) describes the entire rate-temperature curve, since it takes into consideration both the energy of activation of the luminescent reaction and the denaturation of the enzyme.

A plot of the natural logarithm of the light intensity at low temperatures against the reciprocal of the absolute temperature usually gives a straight line whose slope is the negative of the heat of activation divided by the gas constant. At high temperatures it is necessary to consider the other factors discussed above. Within the biological range of temperatures, $\Delta H\ddagger$ is indistinguishable from the usual μ, unless the pressure is varied.

The action of pressure throughout the entire temperature range (figure 2) may be interpreted readily on the basis of this equation (Eyring and Magee, 1942). At the lower temperatures where the predominant reaction is that leading to light production, pressure will retard the rate, since the reaction proceeds with an increase in volume. On the other hand, at high temperatures the predominant reaction is that of reversible denaturation, and in this case pressure will increase light intensity by shifting the denaturation equilibrium to the side of more active enzyme. At the optimum temperature, pressure affects reactions (19A) and (19B) to approximately the same extent, with the result that very little change in light intensity is observed. The recognition of a reversible thermal inactivation as a major factor in temperature-velocity relations of enzyme-catalyzed reactions raises several points of interest in relation to the optimum temperature of various species, the action of drugs, etc. (Johnson, Brown, and Marsland, 1942a). These ideas have been extended in several recent papers (Johnson and Schneyer, 1944; Johnson, Eyring, Steblay, Chaplin, Huber, and Gherardi, 1945). It is of interest that recently Johnson and Campbell (1945 and 1946) demonstrated that high hydrostatic pressures opposed the denaturation of purified human serum globulin at 65°C.

Since alcohol, urea, and other substances are known to influence the reversible denaturation of

isolated proteins, it was considered likely by Johnson, Brown, and Marsland (1942b) that various inhibitors would reversibly affect luminescence in the same manner. Furthermore, if the action of the inhibitors were similar to the temperature inactivation, then pressure would be expected to reverse the inhibition. At the optimum temperature, pressure has little effect on the light intensity of a normal bacterial suspension. If the intensity is first reduced by various inhibitors such as alcohol, chloroform, urethane, etc., pressure will largely

that they have a different mechanism of action. Among this group are compounds like sulfanilamide and para-aminobenzoic acid.

After obtaining these results, Johnson, Eyring, and Williams (1942) derived kinetic equations for three types of inhibitors: a Type I—inhibitor combines indiscriminately with both the native and denatured forms of the enzyme; a Type II—inhibitor combines only with the denatured form; and a Type III—inhibitor combines only with the native form of the enzyme (see reaction 19B). The types

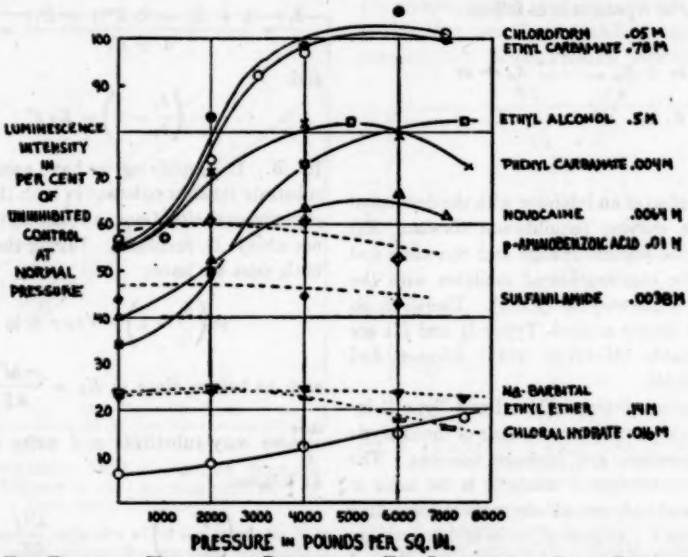
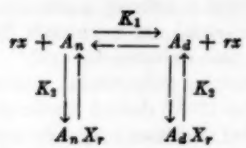


FIG. 3. THE EFFECT OF HYDROSTATIC PRESSURE ON THE INHIBITION OF LIGHT INTENSITY BY VARIOUS INHIBITORS

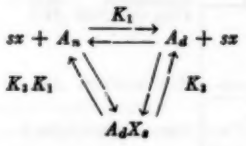
The bacteria, *Ph. phosphoreum*, were suspended in buffered salt solution plus various inhibitors indicated at the right of the curves. Temperature was 17° to 18°C, at which point the pressure alone causes not more than 10% difference in the control intensity. Intensity of light is expressed as percent with respect to a control, without inhibitor, at atmospheric pressure. The curves for inhibitions not sensitive to pressure are indicated by dotted lines. (Johnson, Brown, and Marsland, 1942)

or completely abolish the inhibition. Fig. 3 demonstrates the effect of pressure on the action of various inhibitors. According to the viewpoint adopted above, these substances cause a shift in the reversible denaturation equilibrium in such a way as to reduce the quantity of active enzyme. The pressure effect indicates that this shift takes place with a large increase in volume. Therefore, the inhibitor action is comparable to that observed with high temperature. A second group of inhibitors can reduce the light intensity but their effect is not reversed by pressure. This result indicates

differ according to whether (Type I) the equilibrium established is independent of the denaturation equilibrium, K_1; or (Type II) is directly related to it. The Type I inhibitor combines equally well with A_a and A_d, i.e., at chemical bonds not involved in the reversible denaturation. The reaction with Type I inhibitor may be represented as follows, where x represents concentration of inhibitor, r the number of molecules of x combining with the enzyme molecule, and K_2 the equilibrium constant for the enzyme inhibitor combination:



If an inhibitor combines with an enzyme at bonds made available in the denaturation reaction, then it will promote the temperature inactivation. In this case the inhibitor-enzyme equilibrium, K_3, will be influenced by the value of K_1. Thus Type II may be represented as follows:



The combination of an inhibitor with the denatured form of the enzyme (equilibrium constant K_3) gives the same volume change and the same end results as the combination of inhibitor with the native form of the enzyme (K_1K_3). Therefore, on the basis of kinetic analysis Types II and III are indistinguishable (McElroy, 1943; Johnson and Schneyer, 1944).

The distinction between Type I and Type II inhibitors should be made on the basis of the analysis of the temperature and pressure relations. The effect of conc tration of inhibitor is the same in both types and only reveals the ratio of combining molecules, r or s. In general, a rise of temperature will tend to decrease the inhibition for Type I inhibitors, because of the dissociation of the enzyme-inhibitor complex. With Type II inhibitors, a rise in temperature will also tend to dissociate the enzyme-inhibitor complex; however, in addition there will be a shift toward denaturation, thus making available the chemical bonds with which the inhibitor unites. This will usually result in an increase of inhibition with rise in temperature, and for this reason the optimum will usually shift to a lower temperature.

For a Type I inhibitor we can rewrite equations (19C) and (20), for now the total enzyme g is comprised as follows (omitting brackets indicating concentration):

$$\begin{aligned} g &= A_n + A_d + A_n X_r + A_d X_r \\ &= A_n + K_1 A_n + K_2 A_n X^r + K_1 K_2 X^r \\ &= A_n[1 + K_1 + K_2 X^r(1 + K_1)] \end{aligned}$$

Therefore

$$A_n = \frac{g}{1 + K_1 + K_2 X^r(1 + K_1)}$$

Thus equation (19C) becomes:

$$I_2 = \frac{sk_2 LH_2 g}{1 + K_1 + K_2 X^r(1 + K_1)} \qquad (30)$$

where I_2 equals intensity of light in the presence of a Type I inhibitor. If now we divide equation (20) by equation (30) and simplify, we obtain

$$\frac{I_1}{I_2} = \frac{1 + K_1 + K_2 X^r(1 + K_1)}{1 + K_1} = 1 + K_2 X^r$$

and

$$\left(\frac{I_1}{I_2} - 1\right) = K_2 X^r \qquad (31)$$

[N. B. In simplifying we have assumed that the substrate remains constant in both the control and experimental situations, an assumption that may not always be justified.] Taking the logarithm of both sides we have:

$$\ln\left(\frac{I_1}{I_2} - 1\right) = r \ln x + \ln K_2 \qquad (32)$$

and, as before, since $\ln K_2 = \frac{-\Delta F_2}{RT} = \frac{-\Delta H_2}{RT} + \frac{\Delta S_2}{R}$ we may substitute and write equation (32) as follows:

$$\ln\left(\frac{I_2}{I_1} - 1\right) = r \ln x - \frac{\Delta H_2}{RT} + \frac{\Delta S_2}{R} \qquad (33)$$

Therefore, if we plot $\ln\left(\frac{I_1}{I_2} - 1\right)$ against $\frac{1}{T}$ we should, for a Type I inhibitor, obtain a straight line with a slope of $\Delta H_2/R$ (the heat of reaction of enzyme with inhibitor). A plot of $\ln\left(\frac{I_1}{I_2} - 1\right)$ against $\ln x$ should give a straight line whose slope equals r, the number of inhibitor molecules combining with the enzyme. Knowing the values for r, x, and ΔH_2, we may calculate the entropy change by substitution.

By the same reasoning the equation for a Type II inhibitor is as follows:

$$\ln\left(\frac{I_1}{I_2} - 1\right)\left(1 + \frac{1}{K_1}\right) = s \ln x - \frac{\Delta H_3}{RT} + \frac{\Delta S_3}{R} \qquad (34)$$

Therefore, if we plot $\ln\left(\frac{I_1}{I_2}-1\right)\left(1+\frac{1}{K_1}\right)$ against $\frac{1}{T}$, we should for a Type II inhibitor obtain a straight line with a slope of $\Delta H_2/R$, and by a similar plot using $\log x$ as the abscissa we should obtain s, the number of inhibitor molecules combining with the enzyme. It will be noted that for this type of inhibitor, consideration is given to the equilibrium constant between the native and denatured forms of the enzyme. Knowing the heat of denaturation and the entropy change found from equation (23), it is possible to obtain values of K_1 for various temperatures, using the following relationship:

$$K_1 = e^{\frac{-\Delta H}{RT}} e^{\frac{\Delta S}{R}}.$$

From equations (32) and (34) it is obvious that only in the former case does one obtain the true equilibrium constant between enzyme and inhibitor when the log of the activity is plotted against the log of the concentration of inhibitor. This is true also of all the other methods of plotting which were discussed in the previous section.

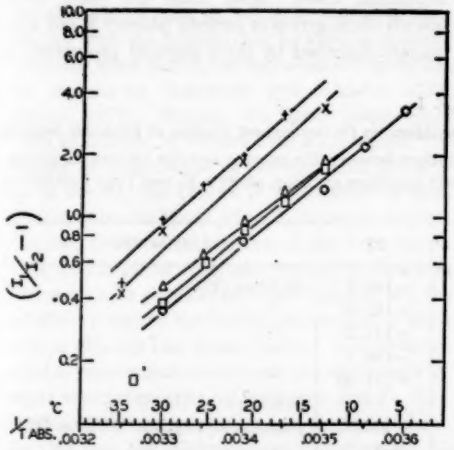


FIG. 4. TEMPERATURE RELATION OF THE SULFANILAMIDE INHIBITION OF LUMINESCENCE IN DIFFERENT SPECIES

Plot for Type I inhibitor. The slopes of the lines indicate the heats of reaction for the equilibrium between the enzyme and sulfanilamide. *V. phosphorescens*, plus and cross marks; *P. phosphoreum*, circles; *A. harveyi*, triangles; *A. fischeri*, squares (Johnson, Eyring, and Williams, 1942).

A test of various inhibitors has been made using the luminescent system, and Figs. 4 and 5 demonstrate a typical analysis of Type I and II inhibitors respectively. In Table 1 results of studies of the effect of inhibitors on the luminescent reaction are tabulated according to their type of inhibition. The heats of reaction and entropy changes are given. It is clear that the Type II inhibitors show large heats of reaction and large entropy changes.

Although no distinction between competitive and non-competitive inhibitors has been made in the present type of kinetic analysis, it is interesting to note that some Type I inhibitors are regarded as competitive. Since Type I inhibitors combine with bonds not involved in the reversible denaturation, it might be supposed that they combine in somewhat the same manner as the substrate or prosthetic group reacts with the apoenzyme. Stated otherwise, it might be expected that many competitive inhibitors will behave according to the Type I reaction.

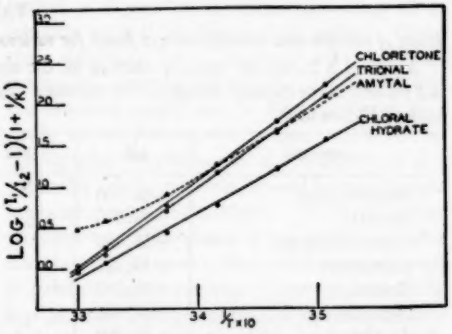


FIG. 5. TEMPERATURE RELATIONS OF THE INHIBITION OF LUMINESCENCE IN *A. FISCHERI* BY VARIOUS NARCOTICS

The data are plotted as described in the text for a Type II inhibitor (combination of the inhibitor with the denatured form of the enzyme). (McElroy, 1943)

The above theory concerning the mechanism of action of inhibitors is of special interest when compared to previous theories of narcosis. As has been pointed out previously, the parallelisms between lipoid affinity (Meyer-Overton theory), lowering of surface tension or adsorption (Traube's rule), water solubility (Richet's rule), etc., do not constitute theories of the actual mechanism of narcotic action. In many cases, especially in the homologous series of polar-non-polar compounds, these various physico-chemical properties may be

related to one another. It can be shown, for example, that when a substance is distributed in equilibrium between two immiscible phases the partition coefficient, k, is given by the following expression: $\ln k = (\bar{F}_{II} - \bar{F}_I)\frac{1}{RT}$ where $\bar{F}_I$ and $\bar{F}_{II}$ are the partial molar free energies of the substance in its standard states in phases I and II respectively. Thus a plot of the logarithm of the partition coefficient against $\frac{1}{T}$ will give a straight line whose slope equals the difference in partial molar free energy ($\Delta\bar{F}$) in the two states. Ferguson (1939) has demonstrated that a logarithmic plot of the partition coefficient against the number of carbon atoms in a homologous series gives a straight-line relationship. This relationship is to be expected, and it simply means that there is a constant increment for each successive homologue in partial molar free energy difference in the two phases. This same relationship is also well known for anaesthetic potency, where it has been demonstrated that equinarcotic concentrations decrease in a definitely quantitative manner as the homologous series is ascended (Richardson's rule). As Ferguson has further pointed out, the other physical constants show an approximately equal change on passing from one member of a series to the next. There are, therefore, several properties which behave similarly to the narcotic concentrations. These include water solubility, partition coefficient, capillary activity, and vapor pressure. If the logarithm of such properties are plotted against the number of carbon atoms in a homologous series such as that of the primary alcohols, it is found that the points lie on a straight line and are essentially parallel to the narcotic or toxic concentration. If an equilibrium exists between the external and internal phases this indeed ought to be the case, since all the above mentioned constants are expressions of a distribution between heterogeneous phases (Ferguson, 1939; Hurst, 1943; Ing, 1943; Schulman, 1943). Since there are many compounds whose action or narcotic potency is not adequately described by these physical properties, it should not be overlooked that these physical properties may be related to the theory of protein denaturation described above. As the results of Table I indicate, all those compounds whose partition coefficient, surface activity, etc., decrease with temperature (such as benzamide, salicylamide, etc.) are in the category of Type I inhibitors, and those whose distribution characteristics increase with temperature (alcohol, chloral hydrate, trional, chloretone, etc.) are of Type II. Thus it would appear that those compounds whose partition coefficient, surface activity, etc., increase with a rise in temperature influence the denaturation of proteins. It is not surprising that such a relationship should be found, since many of these physical properties are known to be important factors in determining protein denaturation. It should be

TABLE 1

Heats of reaction and entropy changes found for various inhibitors on the luminescent reaction in luminous bacteria

ΔH_1 and ΔH_2 are the heats of reaction for the equilibrium between the enzyme and the various inhibitors. ΔS represents the entropy change for the reaction. Type II inhibitors are listed under ΔH_1 and Type I inhibitors under ΔH_2 (see text).

INHIBITOR	ΔH_1	ΔH_2	ΔS	REFERENCES
Phenobarbital	−44,160		−146.5	McElroy (1943)
Barbital	−46,000		−152.8	"
Chloral Hydrate	−36,800		−122.0	"
Chloretone	−49,200		−166.5	"
Trional	−48,760		−171.30	"
Alcohol	−37,000		—	Johnson *et al.* (1945)
Urethane	−55,000		−165.00	Johnson, Eyring, and Williams (1942)
Sulfanilamide		−16,980	−42.2	"
Para-aminobenzoic acid		−18,200	−50.00	"
Benzamide		−11,960	−40.1	McElroy (1943)
Salicylamide		−18,860	−65.8	McElroy (1943)

emphasized, however, that these properties of molecules may be significant not only in the mechanism of penetration and concentration at the site of action, but also in the actual mechanism of action. The means by which a compound penetrates the cell membrane may, then, be a direct measure of its narcotic potency or mechanism of action. This is to be expected if the proteins are closely associated with the lipoids of the cell to form a lipo-protein complex in much the same way as has been postulated for the cell membrane. If the inhibitors penetrate or orient themselves in the lipoid phase by polar as well as by non-polar association, then the proteins may be affected in somewhat the same manner as that observed in studies on monolayers (Langmuir and Schaefer, 1938; Rideal, 1945). Namely, the lipoid phase would tend to increase in volume with a subsequent unfolding or denaturation of the associated proteins. As is known, this process of penetration of compounds into the lipoid phase is pressure sensitive (Rideal, 1945). Furthermore, it has been shown that the inhibition of certain enzymes by narcotics decreases with purification of the enzyme, but the sensitivity may be restored by the addition of albumin or globulin (see Höber, 1945). If compounds tend to penetrate or concentrate at surfaces only by polar association (i.e., by hydrogen bonds), then there would be no penetration into the lipoid phase. In this case the inhibition would presumably be either by displacement of the protein from the interface or by combination with polar groups in the protein itself. It is to be remembered, however, that when numerous compounds are studied for their narcotic potency or action, consideration must be given not only to molecular structure and weak intermolecular forces, as in the cases above, but also to chemical reactivity, ionization, etc., all of which may be expected to influence the mechanism of inhibitory action.

Thus far the supporting evidence for the denaturation theory has been obtained primarily from experiments using the luminescent reaction. The various assumptions which have been made in the derivation of the kinetic equation for this system *in vivo* have been discussed elsewhere (Anderson and Chase, 1944; McElroy, 1944a; McElroy and Ballentine, 1944; Johnson, Eyring, *et al.*, 1945). Further work will be necessary before a general statement can be made as to the mechanism of inhibition in other systems. The present theory cannot be expected to furnish an answer to the problem of the specificity of inhibition which the narcotics demonstrate *in vivo* and, therefore, the theory is not primarily concerned with the site of action, which again is an important aspect of a general theory of narcosis. Here lipoid constituents of the cell may again be important in maintaining a critical concentration of a particular inhibitor at a specific site according to the laws governing distribution.

SITE OF ACTION AND THE INFLUENCE OF INHIBITORS ON CELLULAR ACTIVITY

In isolated enzyme systems wherein the various components of the reaction can be rigorously controlled, it is possible to restrict the study of an inhibitor to a single phase of its action. Under these conditions one is concerned with the actual mechanism whereby the enzyme is inhibited, and the observed results can be directly related to a single component of the system. However, in dealing with the mechanism of the inhibition of a particular cellular response, several factors of prime importance must be considered. In all probability the fundamental processes of inhibition of cellular functions are the same as those inhibitions observed in isolated enzyme systems. However, it must be kept in mind that because of the intricate balance of the enzyme-catalyzed systems in the living cell, inhibition or disruption of cellular processes may occur for reasons that are not observable on a single isolated system. Therefore, because of the structure of cells and tissues, several important factors must be considered as fundamental to the understanding of the mechanism of inhibitory action irrespective of the mechanism of inhibitory action on isolated enzymes. (See Borei, 1945.)

A. The Relation of Permeability to the Mechanism of Inhibitory Action

It is unnecessary in the present review to discuss all of the factors known to affect the entrance of substances into normal cells. Recent monographs and books on the subject have adequately summarized the available data, and the reader is referred to them for further details (Davson and Danielli, 1943; Heilbrunn, 1943; Höber, 1945). However, a brief mention will be made of some of the more important factors that have been consistently overlooked in recent studies.

In some cases of inhibitory action the entire problem may be one related to the interference with penetration of normal metabolites. This is particularly true in those cases wherein active metabolic transfer of essential substances occurs and in which the possibility exists that the inhibition of this transfer system limits certain physiological processes. Inhibition of the absorption of various compounds such as riboflavin, glucose, etc., from the intestine is probably related to such a mechanism of action. It may be true that eventually the responsibility for this inhibition will be traced to a particular enzyme system, and the specific nature of the inhibition determined. At present, however, the inhibition of absorption offers a possible explanation of the difference in susceptibility of organisms to a particular compound. Thus an inhibitor which possibly prevents the active transport of an essential compound across the cell membrane might not interfere with its utilization, once inside. Such an interpretation may be used to explain several published accounts of inhibition (see Roblin, 1946). For example, Mitchell and Houlahan (1946), in their studies of the mutant of *Neurospora* requiring riboflavin for growth, found that lumichrome and lumiflavin inhibit the utilization of added riboflavin. This finding is not surprising, because of the similarity of these compounds to riboflavin itself. However, neither lumichrome nor lumiflavin inhibits the growth of the wild type organism, which is able to synthesize its own riboflavin. It may be, then, that riboflavin must be transferred actively across the membrane (possibly by phosphorylation), and that lumichrome or lumiflavin interferes with this process. Once the riboflavin is inside the cell, the inhibitors are not effective in interfering with its function. An inhibition of this type is of interest from the standpoint of comparative physiology. It points out the important possibility of obtaining specific metabolic inhibitors. A similar explanation is possible even in the absence of the penetration factor. If added riboflavin, as such, is not the normal biological precursor to those intracellular compounds which require it as part of their structure, a new reaction is necessary to convert riboflavin to the normal intermediate. This different reaction offers a new site for an inhibition and would, therefore, make a difference in the response to a particular compound between the mutant and wild type organisms.

The factor of permeability is also important whenever a particular compound must penetrate the cell membrane in order to produce its effect. Several factors, important in this respect, have been adequately reviewed previously. In considering ionizable compounds, it is important to determine whether the substance penetrates in the molecular or ionic form, or both. The extensive experiments of Krahl and Clowes (1936, 1938, 1940) on the effect of substituted phenols on the respiration and cell division of sea urchin eggs demonstrate this point. They have found that various phenols penetrate the fertilized eggs of *Arbacia punctulata* only in the form of undissociated molecules. Furthermore, the inhibition of cell division is dependent on the concentration of phenol molecules in the medium and is independent of the concentration of phenol anions in the medium. Thus it was possible to vary the molar concentrations of the various phenols considerably, yet to obtain the same degree of inhibition of cell division, provided the pH of the medium was so adjusted as to give the same number of undissociated molecules.

This same dissociation factor appears to be important in relation to the action of various sulfonamides. Several workers have observed a relationship between the degree of dissociation of sulfonamides and their bacteriostatic action. Cowles (1942) and Bruechner (1943) found that maximum bacteriostatic effect was obtained when the sulfonamides they studied were approximately 50 per cent ionized. Cowles suggested that the sulfonamides penetrate the cell membrane only in the form of the undissociated molecules. Once inside the cell, however, the ionized form is responsible for the antibacterial action. Therefore, it would be expected that the maximum activity of a particular sulfonamide would fall near a point where its pK_a equals the pH of the medium.

Subsequently, Kumler and Daniels (1943) suggested that the reason for the maximum in the bacteriostatic activity—pK_a curve found by Bell and Roblin (1942) for the *N'* mono-substituted sulfanilamides is due to the greater penetrability of the neutral molecule. Whether this can entirely explain the results of Bell and Roblin is not at all certain at present, but there appears little doubt that it is of some importance. It is interesting, in this connection, that Wyss, Lilly, and Leonian (1944) demonstrated that pH has a great effect on the utilization of para-aminobenzoic acid by *Neurospora crassa*. Using the 'aminobenzoicless' mu-

tant of *Neurospora*, they demonstrated that the effectiveness of PABA as a growth factor decreases with an increase in pH. However, once this mutant strain spontaneously reverted to its own synthesis of PABA, it was found that pH had very little effect. Since the acid dissociation constant of PABA is approximately 2×10^{-5}, it would be expected that as the pH increases above this value the availability of PABA would decrease as found, assuming that only the molecular species penetrates. On the other hand, once PABA is past the membrane the pH would have no more effect on the mutant than on the wild type organism. Although there are alternate explanations, it would appear that the above view is justified on the basis of numerous other findings in the field of cell permeability. Therefore, the nature of the penetrating molecule must be considered important when analysing the mechanism of inhibitory action. The reports that one molecule of a particular substance can antagonize twenty thousand or more of another may be explained in part by such a mechanism as this.

Still other factors are of importance for the entrance of substances into cells. Some of these factors, such as lipoid solubility, surface activity, etc., can be related thermodynamically to one another and need not constitute independent factors. As is well known, lipoid solubility decreases with degree of ionization; and, as pointed out previously, this may be expected to be important, not only in the mechanism of penetration of a compound, but also in its mechanism of inhibitory action. The actual size or shape of a molecule, as is well known, will influence its entrance into a cell or its access to the site of action. This, too, is important not only from the standpoint of entrance, but also in relation to the actual mechanism of action. More and more the sizes and shapes of molecules are coming to be recognized as important factors in cellular metabolism (Rideal, 1945; Pauling, 1946).

B. Selective Action of Inhibitors on Cellular Processes

In general, both the specific and non-specific inhibitors appear to affect certain aspects of cellular function before others. In many cases this appears to be due not to a high sensitivity of any particular enzyme system, but rather to the delicate integration or coupling of several different systems. The narcotics, which are supposed to be highly non-specific in their inhibitory action when studied on isolated enzyme systems, show a fairly high degree of specificity when certain aspects of cellular function are considered. Urethane, for example, will inhibit many of the well-known dehydrogenases concerned in the breakdown of carbohydrates; yet it fails to affect oxygen consumption *in vivo* in concentrations sufficient to inhibit cell division completely (see Elvehjem, Wilson, *et al.*, 1939).

Numerous investigators have studied this selective action of inhibitors on cellular processes (see Korr, 1937; Ballentine, 1940; Stannard, 1941; and Fisher, 1942). Stannard (1939a, b) observed that the oxygen consumption of resting frog muscle is relatively insensitive to azide, in contrast to its sensitivity to cyanide. On the other hand, the increased oxygen consumption caused by chemical or electrical stimulation is markedly sensitive to this agent. Since the oxygen consumption of the unstimulated resting muscle is not affected by azide, Stannard concluded that the oxidative metabolism initiated by the activity of contraction is mediated by a respiratory chain different from that operating in the resting muscle. Of interest, however, is the fact that in low concentrations azide not only fails to inhibit but actually stimulates the oxygen uptake of the resting muscle. The cause of the stimulation of oxygen uptake was found to be slow contracture. Contracture also occurred at high concentrations of azide, even where no increase in oxygen consumption was apparent. It was further demonstrated that with azide, under anaerobic conditions, there was first an absorption of CO_2 (associated with phosphocreatine breakdown) followed by a greatly augmented rate of CO_2 production (due to the formation of lactic acid). Apparently, then, the oxidation of lactic acid is inhibited by azide and, with the breakdown of phosphocreatine to liberate inorganic phosphate, the glycolytic processes are stimulated (see M. Johnson, 1941). The fact that azide will cause a stimulation of oxygen consumption in the "resting" muscle offers a further explanation of an apparent azide-insensitive system that is supposedly different from the system functioning during activity. Reasons for suspecting that the cytochrome system may still function in the presence of azide have been discussed by Ball (1942) and Stotz (1942).

Armstrong and Fisher (1940) have compared the effect of azide and of cyanide on the frequency of the embryonic heartbeat of *Fundulus* and found

in that fish both a cyanide- and an azide-insensitive activity. Their results indicated that there could not be two parallel routes, one cyanide-sensitive and the other both azide- and cyanide-sensitive, for the sum of the activities of the two would amount to 122 per cent of the normal frequency. They concluded that the routes inhibited by these two compounds were either identical, or in series for part of their course (in this connection see Winzler, 1943).

In their studies on the effect of urethane on oxygen consumption and cell division in yeast cells, Fisher and Stern (1942) demonstrated complete inhibition of cell division with only a slight decrease in oxygen uptake. In the kinetic analysis of this inhibition they assumed, as have others, that an inhibitor, N, combines reversibly with an enzyme, E, according to the following equation:

$$E + aN \rightleftarrows EN_a. \tag{35}$$

The symbol a here indicates the number of units of narcotic which combine or react with one unit of enzyme. According to the mass law, at equilibrium:

$$\frac{[E][N]^a}{[EN_a]} = K. \tag{36}$$

By rearranging and taking logarithms, equation (36) becomes:

$$\log \frac{[E]}{[EN_a]} = \log K - a \log [N]. \tag{37}$$

If U (uninhibited) represents the rate of reaction in the presence of a given inhibitor, and I (inhibited) represents the difference between U and the normal rate, then U/I is equal to E/EN_a. Therefore equation (37) becomes:

$$\log \frac{U}{I} = \log K - a \log [N]. \tag{38}$$

It is evident that equation (38) is the same as equation (32), except that U/I is the reciprocal of $(I_1/I_2 - 1)$ and, therefore, if log U/I is plotted against log $[N]$ a straight line should result whose slope is equal to a, the number of inhibitor molecules combining with the enzyme. According to the previous discussion, however, the intercept will give the true equilibrium constant only if a Type I inhibitor is being employed: i.e., if the inhibitor does not influence the equilibrium between the native and denatured forms of the enzyme (see equation 34). Temperature and pressure studies are necessary to determine this point. However, Fisher and Stern's analysis does not make use of this constant, but solely of the slope of the resulting line. They found that upon plotting the data for oxygen consumption at various concentrations of urethane, according to equation (38), the points did not fall upon a single straight line, but rather upon two straight lines as shown in Fig. 6. From these data the authors postulated that the total

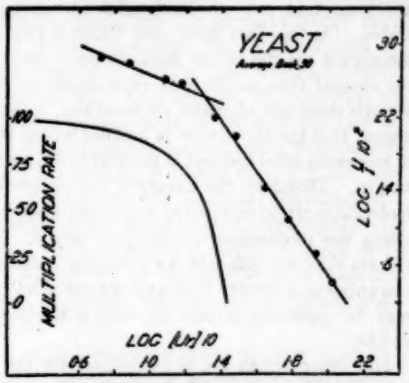


FIG. 6. THE EFFECT OF URETHANE ON OXYGEN CONSUMPTION AND CELL DIVISION IN YEAST

Concentrations are expressed as grams in 100 mls. of solution. The dots are the averages of four experiments on respiration, the data being plotted to test the validity of equation (38) in the text. The smooth curve represents the average rate of cell division in four experiments expressed as a percentage of the control rate. (Fisher, 1942)

oxygen consumption of the cells results not from a single chain of oxidative reactions, but instead from two such chains whose courses are parallel and independent. There would then be two equations having the form of equation (38), one for each of these reactions; and according to the results, one system (A) is far more sensitive to the inhibitor than the other (B). At low concentrations of urethane only system A is inhibited, and as the concentration of urethane rises inhibition of A approaches completion before any inhibition of system B occurs. All functions of the cell which depend on the activity of system A will be inhibited to a greater degree by low concentrations of urethane than those functions which are related to system B. From Fig. 6 it will be noted that cell division is completely inhibited at the concentration marked by the intersection of the two lines. Inhibition of cell division thus parallels inhibition of system A. Fisher and Stern suggest that sys-

tem A be called the "activity" system, since it is associated with cell division, to distinguish it from the "resting" system, which is affected in this case only at higher concentrations of the inhibitor. This terminology is essentially that proposed by Stannard (1939a) for the metabolism of active and resting muscle.

Fisher and Henry (1944) have published similar results for the effect of urethane and chloral hydrate on sea urchin eggs. The effect of the narcotics on the oxygen consumption of unfertilized eggs indicates that only one oxidative system functions prior to fertilization. When similar observations were made on fertilized and therefore

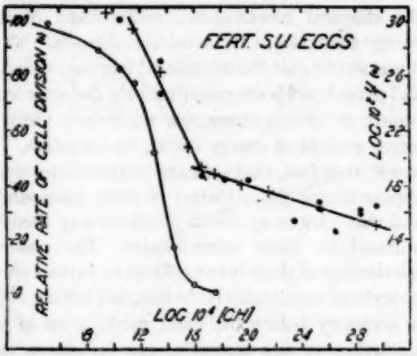


FIG. 7. THE EFFECT OF CHLORAL HYDRATE ON OXYGEN CONSUMPTION AND CELL DIVISION IN THE FERTILIZED SEA URCHIN EGG

Description same as for Figure 6. Chloral hydrate concentration is expressed as molar solution. (Fisher and Henry, 1944)

dividing cells, the results were quite different. With the initiation of cell division an "activity" system is added to the resting system already present in the unfertilized egg, and the inhibition of this activity system parallels the inhibition of cell division (Fig. 7). Ormsbee and Fisher (1944) have reported similar results for the effect of urethane on the oxygen consumption and rate of cell division in the ciliate *Tetrahymena geleii*.

Krahl and Clowes (1940) have studied the effects of various substituted phenols on the respiration and cell division of sea urchin eggs and found slightly different results from those obtained with the narcotics. They observed that with various low concentrations of phenols the respiration of both fertilized and unfertilized eggs is greatly stimulated and that, at the concentration which gives maximum stimulation, cell division is completely, but reversibly, inhibited. Fig. 8 demonstrates the effect of three substituted phenols. This stimulated respiration is completely cyanide-sensitive. Krahl and Clowes have suggested that here the inhibition of cell division is due to an interference of some oxidation-reduction or phosphorylating steps associated with the cyanide-sensitive respiratory system. It is interesting that this is comparable to the dependence of the Pasteur reaction in certain tissues on an oxidative step that is poisoned by the substituted phenols. Clowes and Krahl (1940) further observed, however, that with phenyl urethane, cell division is 50 per cent in-

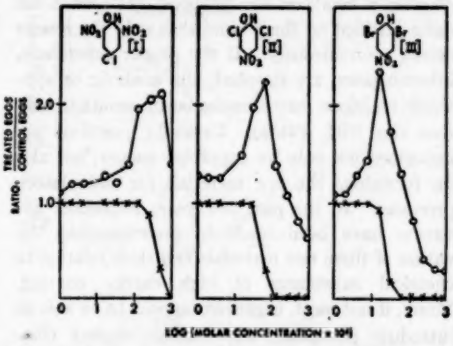


FIG. 8. STIMULATION OF OXYGEN CONSUMPTION AND BLOCK TO CELL DIVISION OF FERTILIZED *ARBACIA* EGGS PRODUCED BY VARIOUS CONCENTRATIONS OF SUBSTITUTED PHENOLS AT 20°C

(I) 2,6-dinitro-4-chlorophenol, (II) 2,6-dichloro-4-nitrophenol, (III), 2,6-dibromo-4-nitrophenol. Reagents were added 25 minutes after fertilization. Circles describe oxygen uptake, and crosses represent cell division. (Krahl and Clowes, 1936)

hibited at a concentration at which oxygen consumption is 130 per cent of the control.

It may be that in this case a particular oxidative step has been inhibited, but the over-all respiration has been greatly stimulated and therefore masks the true results. The production of light in luminous bacteria represents such an example. It is possible to inhibit luminescence, which is an oxygen-consuming reaction, and yet the total oxygen consumption may remain the same or even in some cases be greatly stimulated. Here there can be little doubt that one particular oxidative step has been blocked, yet over-all oxygen consumption does not reveal it. *In various organisms it would appear, then, that cell division and other activities can be inhibited by very low concentrations of in-*

hibitors that may depress only slightly, or even stimulate, oxygen consumption.

C. Effect of Inhibitors on Oxidative and Fermentative Assimilation

The greater apparent sensitivity of all the processes concerned with the activity system appears to be related to the fact that these processes are "synthetic" reactions. They are customarily considered as energy-consuming reactions (endergonic) and therefore as necessarily coupled with energy-yielding steps (exergonic). From the results of recent studies made on microorganisms, it would appear that the general division of metabolism into essentially catabolic and anabolic reactions is not quite justified on the ground that only the former occurs spontaneously. If the proper substances, intermediates, are supplied, the anabolic or synthetic reactions may likewise occur spontaneously (see van Niel, 1943a). Catabolic reactions are important not only for supplying energy, but also for furnishing the raw materials for assimilatory processes. In the past few years important advances have been made in understanding the nature of these raw materials and their relation to chemical substances of high energy content. Many, if not most, organisms appear to be able to introduce phosphate into various organic compounds and then, by a subsequent series of reactions (oxidation-reduction, dehydration, decarboxylation), to raise the potential energy of the phosphate ester linkage. Energy normally lost as heat then becomes stored in the ester linkage as "phosphate bond energy" (Lipmann, 1941; Kalckar, 1941). The resulting compounds may now enter into and in fact may even force synthetic reactions; furthermore, the reaction proceeds spontaneously, i.e., with a liberation of energy. Some of the more interesting examples of such reactions are those concerned with the fixation of carbon dioxide (see Werkman and Wood, 1942; Vogler and Umbreit, 1942; van Niel, 1943b; Lipmann and Tuttle, 1945).

Since the early studies of Barker (1936), Giesberger (1936), and Clifton (1937), numerous investigators have presented evidence that an assimilatory process may accompany oxidation of various simple substrates such as ethyl alcohol, glycerin, glucose, the lower fatty acids, and others. Furthermore, this primary assimilation has been observed with washed, non-proliferating organisms. Barker observed that the colorless alga, *Prototheca zopfii*, oxidized to carbon dioxide and water only a small proportion of each substrate, the remainder being converted into some cellular material of the approximate composition of carbohydrate. Other investigations demonstrated that not only oxidative assimilation, but also fermentative assimilation, is widespread among organisms (see Winzler and Baumberger, 1938; van Niel and Anderson, 1941; van Niel and Cohen, 1942). The exact mechanism of this primary assimilation is not clear, but the existing evidence indicates that certain important intermediates are formed and are necessary for the occurrence of further assimilatory processes. Of importance in this respect is the fact, demonstrated by Clifton and Logan (1938, 1939) that assimilatory reactions are functions of the chemical constitutions, rather than of the energy available, in the substrate molecule. Thus it was shown that the assimilated fractions of lactic and pyruvic acids are quantitatively the same with respect to carbon atoms, yet the former yields a larger amount of energy during its oxidation. It seems, therefore, that primary intermediates must appear during the oxidation of these compounds, and that various synthetic reactions may then be initiated by these intermediates. The possible relationship of these intermediates to various phosphorylated compounds is obvious, but further work is necessary before the exact mechanisms of assimilation, in any organism, can be known (see Lipmann and Tuttle, 1945).

The effect of inhibitors on oxidative assimilation is therefore of great interest in relation to the previously discussed "activity" system. Clifton (1937) observed that acetate is only 75 per cent oxidized to CO_2 and H_2O by washed cells of *Pseudomonas calco-acetica*, but that practically complete oxidation occurs in the presence of low concentrations of sodium azide, iodoacetic acid, and 2,4 dinitrophenol (DNP). He concluded, therefore, that these inhibitors exert a greater degree of inhibition on assimilatory than on oxidative metabolism. Later studies [by Clifton and Logan (1938, 1939) using *E. coli*, Doudoroff (1940) using *Pseudomonas saccharophila*, and Winzler (1940) using yeast] demonstrated a similar effect of various other inhibitors on oxidative assimilation. Clifton and Logan observed that growing cultures of *E. coli* are inhibited by identical concentrations of NaN_3 and DNP, which allow complete oxidation of lactate by washed suspensions. Recently Burris and Wilson (1942) demonstrated that dinitrophenol not only prevents assimilation

in the root nodule bacterium, (*Rhizobium trifolii 205*), but also stimulates the breakdown of stored materials. Thus, in this organism, addition of the inhibitor, after assimilation is complete, produces the same final oxidation of substrate as does an initial addition of DNP. In the root nodule bacteria the assimilated substance, oxidation of which is stimulated by the presence of DNP, is apparently a gum and differs, therefore, from the assimilatory products of other organisms. Clifton and others have failed to observe in other organisms this delayed effect of an inhibitor.

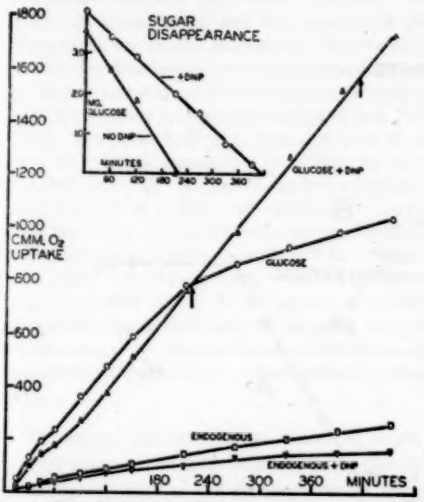


FIG. 9. THE EFFECT OF DINITROPHENOL ON GLUCOSE UTILIZATION BY *R. TRIFOLII* 205
Arrows indicate point of glucose exhaustion from the medium (Burris and Wilson, 1942).

Fig. 9, taken from Burris and Wilson, demonstrates the effect of DNP on the oxidation of glucose by *R. trifolii 205*. Although oxygen uptake is only slightly inhibited, the disappearance of glucose is greatly retarded. Burris and Wilson point out that in many cases the oxygen uptake is stimulated, yet sugar disappearance is still greatly inhibited. Likewise, Clifton and Logan (1939) found that the rate of oxygen consumption in the presence of NaN_3 or DNP, in amounts just sufficient to prevent assimilation, is not markedly different from the rate observed in the absence of the inhibitors.

In luminous bacteria it has been found that various narcotics may inhibit oxidative assimilation in concentrations which tend to stimulate respiration (McElroy, 1944b). This extra oxygen uptake due to stimulation comes not from an increased oxidation of added substrate, but comes primarily from material which has been assimilated during the growth of the organism. The endogenous respiration cannot be inhibited completely even in the presence of a large excess of added substrate, thus indicating that in some way the reserve material may be broken down independently of added substrates. The evidence, however, supports the conclusion that there is a competition for the oxidative pathways. In all probability, the

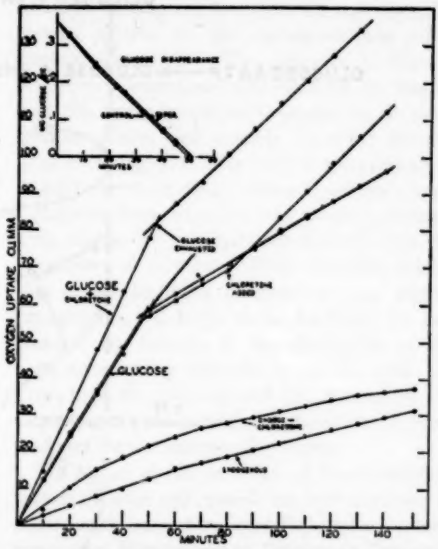


FIG. 10. THE EFFECT OF CHLORETONE ON THE OXYGEN UPTAKE OF LUMINOUS BACTERIA AT 19°C WITH AND WITHOUT GLUCOSE (MCELROY, 1944B).

results merely indicate that the reserve material in the cells is more readily available than the added substrate.

The effect of chloretone on the oxidation of glucose by luminous bacteria is recorded in Fig. 10. Here the uptake of glucose is not markedly affected, yet the oxygen uptake is greatly stimulated. Delayed addition of chloretone increases the rate of oxidation over that of the endogenous respiration, indicating a more rapid utilization of the reserve material. This is also evident from the stimulatory effect of chloretone on the endogenous respiration. This degree of stimulation of endogenous respiration is dependent upon the age of the cells after their removal from the nutrient medium, i.e.,

upon the available reserve material they possess. Light production, an oxygen-consuming reaction, was greatly depressed (75%) by the concentrations of inhibitor used.

Hotchkiss (1944) has recently reported that dinitrophenol prevents phosphate uptake by bakers' yeast respiring in glucose. The concentrations of DNP used were sufficient to prevent any such oxidative assimilation as that reported by Pickett and Clifton (1941, 1943a, b). Similarly, gramicidin, in concentrations that greatly stimulate oxygen uptake, prevents phosphate uptake and assimilation by *Staphylococcus aureus*. Here, too, the degree of stimulation depends upon the quantity of reserve material already present. *Thus, varying with the organism and with the inhibitor, it would appear that oxidative and fermentative assimilation may be prevented by those concentrations of inhibitor that only slightly depress or even greatly stimulate oxidation or fermentation.*

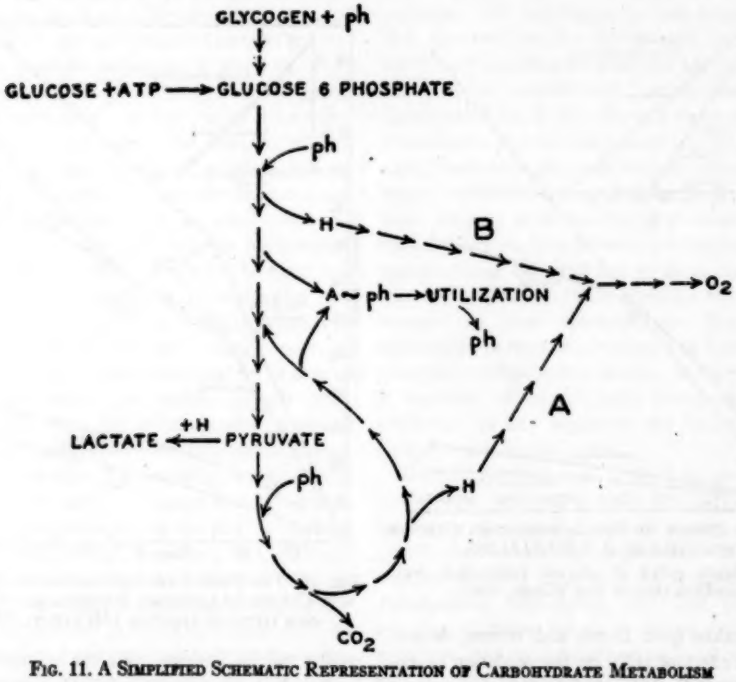


FIG. 11. A SIMPLIFIED SCHEMATIC REPRESENTATION OF CARBOHYDRATE METABOLISM

AN INTERPRETATION OF NARCOTIC ACTION

The similarity of the results by Fisher and his coworkers, by Krahl and Clowes, and by Stannard and others, reported in the previous section, to those results reported in the section on assimilation suggests that the mechanism and site of action of the inhibitors are the same in both cases. From the published accounts of the metabolism of various organisms and tissues it appears possible to develop at the present time certain broad concepts of narcotic action which may be useful and suggestive for future experimentation. These concepts will now be discussed in relation to the generalized scheme of carbohydrate metabolism presented below.

In Fig. 11 a simplified schematic representation of carbohydrate metabolism is presented. This scheme is based upon numerous publications that have been adequately reviewed in the past few years (see Lipmann, 1941; Barron, 1943; and Krebs, 1943). In brief, the decomposition of glycogen to pyruvic acid depends upon the available inorganic phosphate and possibly on an energy-rich phosphate (ATP) not indicated in the scheme. All of the intermediate steps between glycogen and pyruvic acid are reversible. The equilibrium constant of the last step in the formation of pyruvate is such that formation of the latter is greatly favored. The introduction of glucose into the scheme depends upon a high energy source (ATP). Other components being normal, therefore, the rate of decom-

position of glycogen depends upon the inorganic phosphate concentration. The phosphate is introduced into an ester linkage, and subsequently by an oxidation-reduction reaction it becomes an "energy-rich" phosphate ester (*A-ph*). The electrons (hydrogen) removed are transported by various carriers to oxygen (system B). At reduced oxygen tensions or reduced carrier capacity, pyruvate may compete with oxygen for the electrons. Under both anaerobic and aerobic conditions the fate of pyruvic acid depends upon the tissue or the organism (see Stotz, 1945), but in many cases the products of pyruvate metabolism are apparently concerned in numerous "synthetic" reactions. Recent information indicates that these "synthetic" steps involve phosphorylation, and that energy-rich phosphate esters are formed oxidatively. By the process of oxidative decarboxylation, organic phosphate esters are formed and may re-enter the glycolytic chain and force the reaction to synthesis (Lipmann and Tuttle, 1945). Electrons (hydrogen) from this series of reactions are likewise transported to oxygen by various carriers (system A). Apparently oxidative phosphorylation proceeds at a lower concentration of inorganic phosphate than do the glycolytic processes; therefore under limited conditions glycogen will be synthesized from added substrate (glucose, pyruvate, etc.) rather than be broken down. If the process of oxidative phosphorylation is inhibited, the inorganic phosphate will increase to a concentration that will allow a rapid breakdown of synthesized or stored material (glycogen, etc.).

As pointed out previously, Stannard found in resting muscle that azide stimulates the glycolytic processes as well as the consumption of oxygen. The reason for this stimulation was apparently due to the contracture that resulted from the application of the inhibitor. However, the reason for the occurrence of contracture may, in some cases, be related to the inhibition of oxygen-consuming reactions concerned with the maintenance of muscle tone. It is interesting, however, that this stimulated oxygen consumption is observed at azide concentrations that prevent the increased oxygen uptake which occurs following electrical stimulation. It would appear, therefore, that there is both a quantitative and qualitative difference in the source of hydrogen donators, in the presence and absence of azide. In the resting muscle, at least two systems apparently contribute to the total oxygen consumption: (1), the oxygen-consuming reactions associated with the breakdown of glycogen, and (2), those reactions associated with the subsequent oxidation of the intermediates formed. If the latter are partially inhibited in the resting muscle, the former are greatly accelerated. If the latter are completely inhibited, the former still function, but the over-all oxygen consumption is reduced to approximately that of the resting muscle. However, the total oxygen consumption is then dependent upon the glycolytic processes. Since normal hydrogen acceptors accumulate under these conditions, there is again a competition between two systems for the electrons; but in this event one system is oxygen-consuming, and the other is not. The electrons removed in the breakdown of glycogen to pyruvic acid are normally transported to oxygen through the cytochrome system by the coenzymes and other carriers (system B). The pyruvate is likewise oxidatively decomposed and electrons (hydrogen) from this source are carried to oxygen via the cytochrome system, and possibly by other systems (system A, Fig. 11). However, in the presence of an inhibitor which blocks system A, pyruvate is not oxidatively removed, and it may therefore compete with oxygen for the hydrogen derived from the breakdown of glycogen. With increasing inhibition of the hydrogen transport system, oxygen consumption will begin to be inhibited, for two reasons: (1), because of the elimination of the oxygen-consuming reaction concerned with the breakdown of pyruvate, and (2), because of the increasing competition of the accumulated intermediates for the electrons (hydrogen).

The nature of the inhibition of the cytochrome system by azide and cyanide has been discussed at some length by various contributors to a recent symposium (*Symposium on Respiratory Enzymes*). With the lowering by the inhibitor of the electron-transporting capacity of this system, the various intermediates will be relatively more reduced, and in this case the competition is even more accentuated. For a difference in the action of cyanide and azide in this respect, the reader is referred to the important paper of Winzler (1943). Aside from the activity of the cytochrome system and a possible by-pass, maintenance of a residual respiration regardless of the inhibitor concentration may be a measure of the capacity of one of the hydrogen-transporting systems to compete with pyruvic acid. *Therefore, the oxygen-consuming reactions exhibited by normal resting muscle may be entirely different from those which maintain the residual respiration in the inhibited muscle.* The possible mechanism of the stimulation of both fermentation

and oxygen consumption in relation to the above will be discussed below.

It has been pointed out in a previous section that Fisher and his coworkers concluded from their numerous studies that two parallel and independent electron-transporting systems function in normal dividing cells. Although this assumption that two parallel systems contribute to the total oxygen consumption of the dividing cells may be justified, the question cannot be decided with the present type of kinetic analysis, for postulation of two systems in series, rather than in parallel, also leads to the same kinetic equations. Likewise, it is not possible to say definitely that the inhibitor combines at two distinct sites even should two parallel systems exist, provided they have at some point a common step. It is equally plausible to postulate that a common pathway exists, and in that case inhibition at only one site would give the same results. This is due to the fact that the products of the inhibited reaction are not measured directly; therefore, the equilibrium constants of other steps must necessarily enter into consideration. If the metabolism of the cells or tissues takes place by the usual pathway of phosphorylated intermediates, then it is very likely that the removal of electrons at various levels of oxidation-reduction will be mediated by different acceptors (see Fig. 11). Should this be so, the electron-(hydrogen-) transporting systems may be parallel and may actually compete for other electron acceptors such as the cytochrome system; but in any event the electrons represent end products of a reaction chain proceeding in series. However, with this particular system kinetic analysis would indicate that two parallel systems exist, each of which contributes to the total oxygen consumption. For example, under normal "resting" conditions, such as in an unfertilized egg, the rate-limiting process for oxygen consumption is the dehydrogenation of various intermediate substrates. Under these conditions the contributions of electrons by systems A and B to a common electron acceptor (cytochrome-oxygen) would appear by kinetic analysis of oxygen consumption to constitute a single system. If, however, either the activities of system A or B are increased or the active concentration of the common acceptor is decreased by an inhibitor, the presence of two systems may become evident in the kinetic analysis. This is due to the fact that a different system is now rate-determining. With azide it may be possible to limit the cytochrome system in such a way that systems A and B actively compete for the remaining acceptor. If system B is successful, then system A will be depressed. Under these circumstances processes depending upon system A will be inhibited, and the uptake of inorganic phosphate by this system will be eliminated. With more inorganic phosphate available for glycogen breakdown, the activity of system B would increase. With stimulation of system B, pyruvic acid may then be reduced to lactic acid.

In many cases the evidence, which has been put forward for parallel systems, can be explained satisfactorily only by such a scheme. This is true especially for the luminescence reaction, which appears to be highly sensitive to various inhibitors. With cyanide, however, oxygen consumption may be greatly reduced, and yet light production will remain essentially normal. The oxidase, luciferase, concerned in the luminescence reaction is cyanide insensitive, indicating that, in luminous forms at least, a possible by-pass of the cyanide-sensitive part of the cytochrome system exists. Apparently the light-producing system competes with some component of the cytochrome system as electron acceptor, for with a limited glucose concentration it is possible to stimulate light production by the addition of cyanide. Furthermore, with certain inhibitors it appears possible to distinguish at least two systems which contribute electrons to the luminescent system, one which is sensitive to inhibitors, and the other relatively insensitive. For example, in the presence of glucose, low concentrations of dinitrophenol have very little effect on the light production of luminous bacteria. When the glucose is exhausted, however, the light intensity falls immediately to almost zero, whereas normally it would have been maintained at a fairly high level in spite of the exhaustion of glucose, apparently because of the oxidation of accumulated intermediates. In this case, the inhibition of oxygen consumption parallels the inhibition of light intensity. It is interesting, however, that this inhibition of light intensity at the point of glucose exhaustion depends upon the endogenous respiration. For if dinitrophenol is added to freshly harvested bacterial cells without added glucose, the oxygen consumption is stimulated, and light intensity is only slightly inhibited (15–20 per cent). However, once the reserved material has been oxidized, the light intensity is inhibited completely. Therefore, the inhibition

of luminescence at the point of exhaustion of glucose from the medium depends upon whether or not the reserve material has likewise been broken down. In luminous bacteria the reserve material usually has been completely utilized prior to glucose exhaustion. In these organisms, therefore, light intensity as well as oxygen consumption is 90–100 per cent inhibited at the point of substrate exhaustion. This and other evidence indicates that dinitrophenol inhibits the oxidation of intermediate compounds in much the same way that azide apparently inhibits the further oxidation of lactate in muscle. In both cases the inhibition of a particular oxygen-consuming reaction is obscured by an increased rate of breakdown of reserve material.

From what has been said about the effects of various inhibitors on the "activity" metabolism as well as on assimilation, it appears that similar processes are inhibited in both cases. Since in some instances it has been demonstrated that inhibition of assimilation is accompanied by inhibition of phosphate uptake, we may conclude in general that many of the inhibitors which affect cellular activity (assimilation, cell division, etc.) do so by interfering either with the formation or with the utilization of important energy-rich intermediates. That these intermediates are phosphorylated derivatives is indicated by several lines of evidence. With an inhibition of these coupled reactions the metabolism of the organism becomes essentially catabolic. It may be, as Lardy and Elvehjem (1945) suggested, that those agents which speed up metabolism, and at the same time decrease the energy available for work or assimilation, act by allowing oxidations to occur without phosphorylation, or actually cause dephosphorylation of high-energy phosphate compounds. The same mechanism may also work even in those cases where stimulation of oxygen consumption fails to occur, depending a great deal upon the source of the material being oxidized. If the stimulated oxygen uptake is due to a breakdown of material already assimilated, then it seems likely that a release of phosphate by the hydrolysis of energy-rich esters would offer a plausible explanation. It would also offer an explanation for the stimulation of oxygen consumption or glycolysis that is usually observed with concentrations of inhibitors that greatly depress other cellular activities.

The essential effect of such inhibitors, then, may be the rapid breakdown of phosphate esters in much the same way as they are broken down during normal activity. Since the rate of carbohydrate oxidation is limited by the available concentration of inorganic phosphate, the oxidation is normally slow in the resting state (see Fig. 11). With the liberation of inorganic phosphate associated with work (or by the action of an inhibitor), there will be an acceleration of carbohydrate oxidation. If the rate of this liberation of inorganic phosphate exceeds the rate of utilization of substrate in the normal course of carbohydrate breakdown (as in oxidative phosphorylation), the accumulation of phosphate will accelerate the breakdown of glycogen or of other stored material (Johnson, M. J., 1941; Cori, 1941). This is entirely analogous to the explanation offered for the Pasteur effect by M. J. Johnson, in which a lack of oxygen accelerates the breakdown of carbohydrates. The inhibitors apparently check the oxidative steps involved in assimilatory processes (oxidative phosphorylation) and therefore allow a more rapid breakdown of the carbohydrates to lactic acid or some other fermentative end product. Inhibition of this oxidative assimilation may occur, therefore, at one of several places, and depends entirely upon the inorganic phosphate concentration and the competition for the hydrogen acceptors by the glycolytic and the assimilatory processes. In Table II there are recorded several different inhibitors which are known to stimulate the glycolytic or respiratory processes, and yet at the same time inhibit certain "energy consuming" or "synthetic" steps. Thus, Pickett and Clifton observed that DNP prevented assimilation in yeast, yet respiration and glycolysis were stimulated. Ronzoni and Ehrenfest (1936), as well as Cori and Cori (1936b), observed that DNP increased muscle glycolysis while phosphocreatine concentration decreased. The decrease in phosphocreatine content was balanced by an increase in inorganic phosphate. Lardy and Phillips (1943) observed that sperm motility was inhibited by the same agent, yet respiration and glycolysis were stimulated. Krahl and Clowes (1936) observed that cell division was inhibited, while oxygen uptake was greatly stimulated. Dinitrophenol also apparently stimulates the phosphorylation of certain carbohydrates by adenosinetriphosphate (Cori and Cori, 1936a, b; Vandendriessche, 1941). Lardy has observed that the hydrolysis of ATP added to minced rat muscle is increased by DNP (see Lardy and Elvehjem, 1945). In many cases, then, the

stimulation of respiration or glycolysis by DNP can apparently be explained by assuming an increase of inorganic phosphate, which will in turn increase the rate of carbohydrate breakdown. Inhibition of assimilation or activity may then be direct or indirect. If inorganic phosphate is increased greatly by the hydrolysis of some phosphorylated intermediate, then the glycolytic reaction may be so stimulated that the oxidative processes concerned in synthesis may not be able to compete with the available hydrogen acceptors and are consequently inhibited. In many cases the assimilatory processes may proceed normally, and yet with a high internal concentration of inorganic phosphate and with a low one of energy-rich phosphate esters, as postulated, complete breakdown of added substrate may occur. This would be interpreted as an inhibition of assimilation, much as one would interpret the inhibition of phosphocreatine maintenance when demand exceeds the supply.

TABLE 2

A list of a few agents which affect the coupling of oxidation-reduction reactions with energy utilization

INHIBITOR	ORGANISM OR TISSUE	PROCESS STIMULATED	PROCESS INHIBITED	REFERENCE
Phenyl urethane	sea urchin eggs	respiration	cell division	Clowes and Krahl (1940)
Chloral hydrate or chloretone	luminous bacteria	respiration	luminescence and assimilation	McElroy (1944)
Phenobarbital and amytal	luminous bacteria	respiration	luminescence	McElroy (1944)
Various substituted phenols	sea urchin eggs	respiration	cell division	Krahl and Clowes (1936)
Dinitrophenols	frog muscle	respiration & glycolysis	maintenance of phosphocreatine	Ronzoni and Ehrenfest (1936)
"	root nodule bacteria	respiration	assimilation & glucose uptake	Burris and Wilson (1942)
"	sperm	respiration & glycolysis	motility	Lardy and Phillips (1943)
"	yeast	respiration & glycolysis	assimilation	Pickett and Clifton (1943)
"	yeast	respiration & glycolysis	assimilation and phosphate uptake	Hotchkiss (1945)
Azide	yeast	fermentation	assimilation	Winzler (1944)
"	frog muscle	glycolysis & respiration	oxidation of lactate	Stannard (1939)
Gramicidin	Staphylococcus aureus	oxidation	assimilation and phosphate uptake	Hotchkiss (1945)

It is conceivable, however, that in some cases, a true competition by two systems for the hydrogen acceptors may result in an inhibition of one system when the other is stimulated. This would appear to hold true for azide and cyanide inhibition, for with these compounds it is possible to reduce the available hydrogen acceptors. Here competition for the latter is greatly enhanced, the glycolytic

processes apparently being more successful (system B). With the resulting decrease in oxidative assimilation or oxidative phosphorylation there would be an increased amount of inorganic phosphate available for glycolysis, and thus a consequent stimulation. Inhibition of assimilation with complete oxidation of substrate would occur, however, only with concentrations of inhibitors which did not completely suppress system A (Fig. 11). A complete suppression of system A should allow the accumulation of intermediates. This appears to be true in many instances. After the initial breakdown of added substrate, however, it may be possible to utilize the intermediates which have been formed, depending upon the site of inhibition. If this happens, a change in the respiratory quotient, as well as in the rate of oxygen consumption, may be evident throughout the course of substrate utilization. This may explain why azide is such an excellent inhibitor of oxidative assimilation and at the same time allows complete oxidation of substrate. Presumably, with azide system A is not directly inhibited but is depressed, because of the reduced capacity of the cytochrome system.

Recently Album, Tepperman, and Bodansky (1946) have demonstrated a significant decrease of glycogen, phosphocreatine, and adenosine triphosphate in brain tissue taken from rats poisoned by NaCN. The cytochrome oxidase activity of the brain tissue was reduced 50 per cent by the cyanide concentration used. Along with the decrease of the above components there was a corresponding increase in the concentrations of inorganic phosphate, lactic acid, hexose diphosphate, phosphoglycerate, and phosphopyruvate. These results agree with, and support, what has been said concerning the action of various inhibitors on the steps involved in oxidative phosphorylation (see Fig. 11).

The above explanation would appear to be a suitable interpretation of the reported results of inhibitor action in many cases (luminous bacteria, sea urchin eggs, muscle contraction, etc.). It should be emphasized, however, that the postulation of this mechanism does not demand that oxygen uptake be greatly stimulated in all cases. Rate of oxygen uptake depends upon the nature of the oxidizable substrate. If glucose is the added substrate, it may be found that both the uptake and the oxidation of this compound have been inhibited, while the over-all oxygen uptake has been maintained by stimulation of the oxidation of reserve material (Burris and Wilson, 1942). This would be expected if the energy-rich compounds were broken down, for in this case glucose could not be utilized actively, since a high-energy phosphate apparently is necessary for this process. On the other hand, the breakdown of a reserve material such as glycogen would be greatly stimulated, because of the increase of inorganic phosphate inside the cell. All of this may occur without an appreciable uptake of phosphate from the medium, which means that the phosphate already present is sufficient to meet the increased needs due to the more rapid turnover. Thus it is important to know not only the nature of the extra oxygen uptake, but also the relationship of phosphate to substrate uptake. Analogous situations normally exist in various cells. Vogler and Umbreit (1942) found an example in the effect of carbon dioxide on phosphate uptake during sulfur oxidation by sulfur bacteria. In the absence of carbon dioxide, phosphate is taken up by these bacteria during the oxidation of sulfur and is "stored" as energy-rich phosphate. When carbon dioxide is added, the energy-rich phosphate ester is broken down, with a subsequent liberation of inorganic phosphate. In the process carbon dioxide is "fixed" (assimilated) by the cells. It is obvious, however, that any substance which causes a breakdown of energy-rich phosphate will allow a rapid oxidation of added sulfur without further uptake of phosphate. If this breakdown of phosphate esters were sufficiently great, the uptake of carbon dioxide would be inhibited, with a consequent depression of cell division.

It is not suggested that all inhibitors of assimilatory processes possess the same mechanism of action; but those which, in low concentrations, show a selective inhibition of some energy-consuming cellular process have many features in common. The great lability of the energy-rich phosphate esters and the numerous processes by which they may be formed or broken down suggest that they must always be taken into account when considering the over-all mechanism of action of inhibitors of cellular processes. At the same time the lability of the energy-rich esters offers an explanation of why diverse inhibitors appear to affect a variety of cellular processes in somewhat the same fashion, even though the actual site of combination of the inhibitors in the cells may be different.

The usual observation that narcotics inhibit or depress only certain functions or activities, while

having relatively little effect on others, would appear to be due to their effect on "synthetic" processes. Their selective action on the nervous systems of higher forms may be related in part to their favorable distribution in the lipoids, as well as to their interference with energy utilization. Quastel and his associates believe that narcotics exert their effect by inhibiting certain processes in the brain that are required for carbohydrate metabolism, upon which the brain is largely dependent (Quastel, 1939). This explanation of narcosis is supported by the findings of various investigators. Quastel and Wheatley (see Quastel, 1943) found that the narcotics which have greater hypnotic activity also have greater inhibitory power on respiration *in vitro*. Jowett and Quastel (1932) found that concentrations of ether, chlorotone, and evipal which markedly inhibit the oxidation of glucose, lactate, and pyruvate by brain tissue have no effect on the oxidation of succinate. This indicates that the cytochrome system involved in the oxidation of succinate is insensitive to the narcotics. Davies and Quastel (1932) obtained results indicating that the dehydrogenases are relatively insensitive to the action of the narcotics; and Michaelis and Quastel (1941) restricted the site of narcotic action within cells to some system, possibly a flavoprotein, closely associated with the cytochrome system (system A, Fig. 11). Recent results of Greig (1946) further emphasize that this site is sensitive to the narcotics, and her results suggest that the inhibitors selectively inhibit the transfer of hydrogen by cytochrome b, or by some other intermediate having a redox potential similar to that of cytochrome b. These results, together with many others, further emphasize the fact that a highly sensitive system is present, and that it can be related or closely associated to the "activity" system discussed in the previous sections and indicated as A in Fig. 11. A further similarity of the mechanism of action of narcotics on brain tissue to their action on other tissues, following the lines of the previous discussion, is indicated by the results of Fuhrman (personal communication), who has found that the concentration of pentobarbital that gives maximum inhibition of rat brain respiration *in vitro* is the very concentration which gives maximum stimulation of glycolysis.

The actual mechanism of stimulation and inhibition may, therefore, appear to be the same for many inhibitors, whereas the actual site of combination within the cell may be different. As mentioned before, the adsorption of various inhibitors at phase boundaries may shift equilibria for one or more of several reasons (change of dissociation constants, differential adsorption of components, etc.). It may well be that the adsorption of an inhibitor displaces a compound which now becomes active at some other surface. This release may be due to or accompanied by the denaturation of a particular protein. Heilbrunn (1943) has suggested that calcium release is important in the action of narcotics, and has discussed the evidence for the calcium release theory at some length. Possibly such an explanation would suffice to interpret the liberation of phosphate. Since calcium often is combined to form a calcium proteinate, the inhibitors may allow a release of calcium by denaturation. The importance of calcium in the activation of dephosphorylating enzymes is well known.

A more direct action of the inhibitors on the metabolism of particular phosphorylated intermediates may occur, but as yet no studies have been made using this approach, although, as mentioned earlier, Lardy has reported that dinitrophenol stimulates the hydrolysis of adenosine triphosphate by minced rat muscle. The great lability of the energy-rich phosphate esters would indicate that this is a plausible mechanism of action of various inhibitors. The actual inhibition of certain oxidative steps which would prevent the formation of these phosphorylated esters is possible and would appear to explain satisfactorily certain results. In some cases, of course, an inhibitor of certain metabolic processes may really act by catalyzing certain reactions directly or indirectly (through combination with a naturally occurring inhibitor), and thus may successfully eliminate a competing reaction. If, to repeat, the latter reaction is concerned with oxidative phosphorylation, then phosphate uptake by this system would be inhibited and glycolysis would consequently be stimulated by an additional factor induced indirectly by the inhibition (see Fig. 11).

Formulation of a general theory of narcosis or inhibitory action depends upon our knowledge of the metabolic processes of the organisms and tissues employed. On this basis it would appear futile at the present time to attempt such a theory, except in a very broad sense. A plausible and logical scheme of the breakdown of carbohydrates can be presented; but it must be realized that the

data for such a scheme have been derived from several different sources, i.e., from whole organisms, tissue slices, minced tissues, and from enzyme extracts. The generalized scheme used in Fig. 11 to explain the action of various inhibitors is based primarily on published data concerning carbohydrate metabolism, but the relation of fat and protein metabolism to such a scheme is steadily becoming more obvious. The intermediary metabolites of system A (the di- and tricarboxylic acids, acetyl phosphate, etc.) may be regarded as composing a metabolic pool to which all the major foodstuffs contribute and from which they may in turn be regenerated. The action of various inhibitors on this system further suggests that it is a center of great "synthetic" activity. Although it is possible to explain numerous observations on the basis of the selective inhibition of system A, the fundamental mechanism or site of action of inhibitors is still unknown. Only because of the over-all similarity of the metabolism of various cells and tissues do we at present observe a similarity of action on the part of narcotics and of other so-called "indifferent" inhibitors. Further analysis may be expected to reveal differences in the details of their mechanisms and sites of action.

SUMMARY

1. From the standpoint of the actual mechanism of action, as well as the site of action, inhibitors generally may be classified as competitive or non-competitive. In the former category two general types are found: (a) those which compete with substrate for the enzyme; and (b) those which compete with the prosthetic group for the enzymes. In the latter category also two general types are found: (a) those inhibitors which combine with the prosthetic group; and (b) those which combine with the protein portion of the enzyme.

2. It is possible to analyse these various types of inhibitions (competitive and non-competitive) by the use of appropriate kinetic equations. For a competitive inhibition the plot of the reciprocal of the observed velocity of reaction against the reciprocal of the substrate concentration will give diverging lines with a common intercept, for various concentrations of inhibitors. Using a similar plot for non-competitive inhibition, one finds that the intercept as well as the slope increases. The kinetic equations describing the reaction of an enzyme with substrate or inhibitor depend upon the relative concentration of the enzyme and the respective dissociation constants. In this respect three distinct zones of enzyme behavior can be found. In zone A the active enzyme concentration is relatively low, while in zone C the active enzyme concentration is relatively high. Zone B describes intermediate concentrations.

3. Narcotics appear to combine with the protein portion of enzymes non-competitively. The temperature characteristics of this combination indicate that these inhibitors reversibly denature the enzyme. Pressure retards the action of this type of inhibitor.

4. Other theories of narcosis which consider such physical properties as partition coefficient, surface activity, vapor pressure, and water solubility can be related thermodynamically to the above theory of protein denaturation.

5. In a study dealing with the mechanism of inhibitor action the problem of permeability, or ability of the compound to reach the site of action, must be considered.

6. To isolated enzyme reactions the narcotics appear to be indifferent or relatively non-specific, while analysis *in vivo* indicates that certain systems are highly sensitive to these agents. These highly sensitive systems appear to be related to those reactions which normally are considered as synthetic steps.

7. In various organisms, cell division and other activities are inhibited by very low concentrations of inhibitors that may either depress oxygen consumption only slightly or greatly stimulate it.

8. In some cases kinetic analysis indicates that two parallel and independent electron-transporting system exist, with one more sensitive to narcotics than the other. The more highly sensitive of these parallel systems can be related to those reactions which are normally considered as synthetic.

9. If the electrons transported by these two systems represent the end products of a reaction proceeding in series, then it is to be expected that kinetic analysis of the end reaction (as measured by oxygen consumption) would indicate the existence of apparently parallel and independent systems. (See Fig. 11.)

10. Numerous studies indicate that organisms oxidize or ferment a small portion of the substrate furnished them, the remainder being assimilated into cellular components. The evidence indicates that certain important primary intermediates are formed and are necessary for assimilation processes.

Further evidence indicates that these intermediates are probably phosphorylated compounds.

11. Oxidative and fermentative assimilation can be prevented by those concentrations of inhibitor that only slightly depress or even stimulate oxidation or fermentation. The action of the inhibitors in this case is similar to their action on dividing cells, where the division process is depressed with concentrations of inhibitor that have very little effect on respiration or fermentation.

12. In some cases it has been found that phosphate uptake is depressed with concentrations of inhibitors that prevent oxidative or fermentative assimilation. Oxygen consumption or fermentation is usually stimulated by these concentrations of inhibitors.

13. The stimulation of oxygen consumption or fermentation as well as the inhibition of cell division or assimilation by various inhibitors may be interpreted on the assumption that the latter, in some way, cause a breakdown or prevent the formation of various energy-rich phosphate esters.

14. From discussion of the above points a generalized scheme, based primarily upon carbohydrate metabolism, is presented to indicate the possible site and mechanism of action of the narcotics and other "indifferent" inhibitors.

LIST OF LITERATURE

ADAM, N. K. 1941. *The Physics and Chemistry of Surfaces.* Oxford University Press, London.

ALBUM, H. G., J. TEPPERMAN, and O. BODANSKY. 1946. The *in vivo* inactivation by cyanide of brain cytochrome oxidase and its effect on glycolysis and on the high energy phosphorus compounds in brain. *J. biol. Chem.*, 164: 45–51.

AMES, S. R., and C. A. ELVEHJEM. 1944. Inhibition of the succinoxidase system by cysteine and cystine. *Arch. Biochem.*, 5: 191–205.

ANDERSON, R. S., and A. M. CHASE. 1944. The nature of *Cypridina* luciferin. *J. Amer. chem. Soc.*, 66: 2129.

ANSON, M. L., and A. E. MIRSKY. 1934. The equilibrium between active native trypsin and inactive denatured trypsin. *J. gen. Physiol.*, 17: 393.

ARMSTRONG, C. W. J., and K. C. FISHER. 1940. A comparison of the effects of the respiratory inhibitors azide and cyanide on the frequency of the embryonic fish heart. *J. cell. comp. Physiol.*, 16: 103–112.

BALL, E. G. 1942. Oxidative mechanisms in animal tissues. In *A Symposium on Respiratory Enzymes*, [O. Meyerhoff and others]. Univ. Wisconsin Press, Madison.

BALLENTINE, R. 1940. Analysis of the changes in respiratory activity accompanying the fertilization of marine eggs. *J. cell. comp. Physiol.*, 15: 217.

BANCROFT, W. D., and G. H. RICHTER. 1931. The chemistry of anaesthesia. *J. phys. Chem.*, 35: 215.

BARKER, H. A. 1936. Oxidative metabolism of the colorless alga, *Prototheca zopfii*. *J. cell. comp. Physiol.*, 8: 231.

BARRON, E. S. G. 1943. Mechanisms of carbohydrate metabolism. *Adv. Enzymol.*, 3: 149–189.

BEADLE, G. W. 1945. Genetics and metabolism in *Neurospora*. *Physiol. Rev.*, 25: 643–663.

BELL, P. H., and R. O. ROBLIN, JR. 1942. Studies on chemotherapy. VII. A theory of the relation of structure to activity of sulfanilamide type compounds. *J. Amer. chem. Soc.*, 64: 2905–2917.

BERNHEIM, F. 1942. *The Interaction of Drugs and Cell Catalysts.* Burgess, Minneapolis.

BOREI, H. 1945. Inhibition of cellular oxidation by fluoride. *Ark. Kem. Mineral. Geol.*, 20A (8): 1–215.

BRADBURY, F. R., and D. O. JORDAN. 1942. The surface behavior of antibacterial substances. I. Sulfanilamide and related substances. *Biochem. J.*, 36: 287–293.

BROWN, D. E., F. H. JOHNSON, and D. MARSLAND. 1942. The pressure-temperature relations of bacterial luminescence. *J. cell. comp. Physiol.*, 20: 151.

BRUECHNER, A. H. 1943. Sulfonamide activity as influenced by variation in pH of culture media. *Yale J. Biol. Med.*, 15: 813–821.

BURRIS, R. H., and P. W. WILSON. 1942. Oxidation and assimilation of glucose by the root nodule bacteria. *J. cell comp. Physiol.*, 19: 361–371.

CHANCE, B. 1943. The kinetics of the enzyme-substrate compound of peroxidase. *J. biol. Chem.*, 151: 553–577.

——. 1943. The effect of cyanide on the kinetics of the enzyme-substrate compound and overall reaction of peroxidase. *J. cell. comp. Physiol.*, 22: 33–41.

CLARK, A. J. 1933. *The Mode of Action of Drugs on Cells.* Arnold, London.

——. 1937. The action of narcotics on enzymes and cells. *Trans. Faraday Soc.*, 33: 1057.

CLAUDE, ALBERT. 1941. Particulate components of cytoplasm. *Cold Spring Harb. Symp. Quant. Biol.*, 9: 263–270.

CLIFTON, C. E. 1937. On the possibility of preventing assimilation in respiring cells. *Enzymologia*, 4: 246–253.

——, and W. A. LOGAN. 1938. Oxidative assimilation of lactic acid by *Escherichia coli*. *Proc. Soc. exp. Biol. N. Y.*, 38: 619–622.

—, and —. 1939. On the relation between assimilation and respiration in suspensions and in cultures of *Escherichia coli*. *J. Bact.*, 37: 523–540.

CLOWES, G. H. A., and M. E. KRAHL. 1940. Studies on cell metabolism and cell division. III. Oxygen consumption and cell division of fertilized sea urchin eggs in the presence of respiratory inhibitors. *J. gen. Physiol.*, 23: 401–411.

COMMONER, BARRY. 1942. Structural relations in cell respiration. *Quart. Rev. Biol.*, 17: 46–59.

CONE, N. M., S. E. FORMAN, and J. KRANTZ. 1941. Relationship between anesthetic potency and physical properties. *Proc. Soc. exp. Biol. N. Y.*, 48: 461.

CORI, C. F. 1941. Phosphorylation of glycogen and glucose. *Biol. Symp.*, 5: 131–140.

CORI, G. T., and C. F. CORI. 1936a. The formation of hexosephosphate esters in frog muscle. *J. biol. Chem.*, 116: 119–128.

—, and —. 1936b. An unusual case of esterification in muscle. *J. biol. Chem.*, 116: 129–132.

COWLES, P. B. 1942. The possible role of ionization in the bacteriostatic action of the sulfonamides. *Yale J. Biol. Med.*, 14: 599–604.

DAVIES, D. R., and J. H. QUASTEL. 1932. Dehydrogenation by brain tissue: the effects of narcotics. *Biochem. J.*, 26: 1672–1684.

DAVSON, H., and DANIELLI, J. F., 1943. *The Permeability of Natural Membranes*. Cambridge University Press, Cambridge, Eng.

DOUDOROFF, M. 1940. The oxidative assimilation of sugars and related substances by *Pseudomonas saccharophila* with a contribution to the problem of the direct respiration of di- and polysaccharides. *Enzymologia*, 9: 59–72.

EBERSOLE, E. R., C. GUTTENTAG, and P. W. WILSON. 1944. Nature of carbon monoxide inhibition of biological nitrogen fixation. *Arch. Biochem.*, 3: 399–418.

EHRENFEST, E., and E. RONZONI. 1933. Effect of dinitrophenol on oxidation of tissues. *Proc. Soc. exp. Biol. N. Y.*, 31: 318–319.

ELVEHJEM, C. A., P. W. WILSON, et al. 1939. *Respiratory Enzymes*. Burgess, Minneapolis.

EYRING, H., and J. L. MAGEE. 1942. Application of the theory of absolute reaction rates to bacterial luminescence. *J. cell. comp. Physiol.*, 20: 169.

—, and E. A. STEARN. 1939. The application of the theory of absolute reaction rates to proteins. *Chem. Rev.*, 24: 253.

FERGUSON, J. H. 1939. The use of chemical potentials as indices of toxicity. *Proc. roy. Soc.*, B., 127: 387–404.

FILDES, P. 1940. A rational approach to chemotherapy. *Lancet*, 1: 955–957.

—. 1941. Inhibition of bacterial growth by indole acrylic acid and its relation to tryptophane; illustration of inhibitory action of substances chemically related to essential metabolites. *Brit. J. exper. Path.*, 22: 293–298.

FISHER, K. C. 1942. Narcosis. *Canad. med. Assoc. J.*, 47: 414–421.

—, and R. J. HENRY. 1944. The effects of urethane and chloral hydrate on oxygen consumption and cell division in the egg of the sea urchin, *Arbacia punctulata*. *J. gen. Physiol.*, 27: 469–481.

—, and RICHARD ÖHNELL. 1940. The steady state frequency of the embryonic fish heart at different concentrations of cyanide. *J. cell. comp. Physiol.*, 16: 1–13.

—, and J. R. STERN. 1942. The separation of an "activity" metabolism from the total respiration of yeast by the effects of ethyl carbamate. *J. cell. comp. Physiol.*, 19: 109–122.

FREUNDLICH, H. 1937. Colloidal structures in biology. *J. phys. Chem.*, 41: 1151.

GADDUM, J. H. 1943. The antagonism of drugs. *Trans. Faraday Soc.*, 39: 323–333.

GIESBERGER, G. 1936. *Beitrage zur Kenntnis der Gattung Spirillum Ehbg.* Dissert., Utrecht.

GLASSTONE, S., K. J. LAIDLER, and H. EYRING. 1941. *The Theory of Rate Processes*. McGraw-Hill, New York.

GOLDSTEIN, A. 1944. The mechanism of enzyme-inhibitor-substrate reactions illustrated by the cholinesterase-physostigmine-acetylcholine system. *J. gen. Physiol.*, 27: 529.

GREEN, M. W. 1946. Some modern contributions to the enzyme theory of pharmacology. *J. Amer. pharm. Ass.*, 35: 1–5.

GREIG, M. E. 1946. The site of action of narcotics on brain metabolism. *J. Pharm. exp. Therap.*, 87: 185–192.

HAAS, E. 1944. The effect of atabrine and quinine on isolated respiratory enzymes. *J. biol. Chem.*, 155: 321–331.

HALDANE, J. B. S. 1930. *Enzymes*. Longmans, Green, New York.

HARVEY, E. N. 1940. *Living Light*. Princeton University Press, Princeton.

—. 1941. Review of bioluminescence. *Ann. Rev. Biochem.*, 10: 531–551.

HEILBRUNN, L. V. 1943. *An Outline of General Physiology*. 2nd ed. W. B. Saunders, Philadelphia.

HELLERMAN, L., A. LINDSAY, and M. BOVARNICK. 1946. Flavoenzyme catalysis. Inhibition of d-amino acid oxidase by competition with flavin-adenine-dinucleotide of atabrine (quinacrine), quinine and certain other compounds. *J. biol. Chem.*, 163: 553–570.

HENDERSON, V. E. 1930. The present status of the theories of narcosis. *Physiol. Rev.*, 10: 171–220.

HENRY, R. J. 1943. The mode of action of sulfonamides. *Bact. Rev.*, 7: 175–263.

HÖBER, R. 1945. *Physical Chemistry of Cells and Tissues.* Blakiston, Philadelphia.

HOTCHKISS, R. D. 1944. Gramicidin, tyrocidine and tyrothricin. *Adv. Enzymol.*, 4: 153–195.

——. 1946. The nature of the bacterial action of surface active agents. *Ann. N. Y. Acad. Sci.*, 46: 479–494.

HURST, H. 1943. Principles of insecticidal action as a guide to drug reactivity—phase distribution relationships. *Trans. Faraday Soc.*, 39: 390–411.

HUTCHINSON, M. C., and E. STOTZ. 1941. Observations on inhibition of brain respiration and narcosis. *J. biol. Chem.*, 140: LXV.

ING, H. R. 1943. Chemical constitution and pharmacological action. *Trans. Faraday Soc.*, 39: 372–380.

JOHNSON, F. H. 1942. Mechanism of p-aminobenzoic acid and the parallel effects of ethyl carbamate (urethane). *Science*, 95: 104.

——, D. E. BROWN, and D. A. MARSLAND. 1942a. A basic mechanism in the biological effects of temperature, pressure and narcotics. *Science*, 95: 200.

——, ——, and ——. 1942b. Pressure reversal of the action of certain narcotics. *J. cell. comp. Physiol.*, 20: 269.

——, and D. H. CAMPBELL. 1945. The retardation of protein denaturation by hydrostatic pressure. *J. cell. comp. Physiol.*, 26: 43–46.

——, and ——. 1946. Pressure and protein denaturation. *J. biol. Chem.*, 163: 689–698.

——, and A. M. CHASE. 1942. The sulfonamide and urethane inhibition of *Cypridina* luminescence in vitro. *J. cell. comp. Physiol.*, 19: 151.

——, and H. EYRING. 1943. Calculation of enzyme-inhibitor equilibrium constants in relation to changes in optimum temperature. *Fed. Proc.*, 2: 25.

——, and ——. 1944. The nature of the luciferin-luciferase system. *J. Amer. chem. Soc.*, 66: 848.

——, ——, and W. KEARNS. 1943. A quantitative theory of synergism and antagonism among diverse inhibitors, with special reference to sulfanilamide and urethane. *Arch. Biochem.*, 3: 1.

——, ——, R. STEBLAY, H. CHAPLIN, C. HUBER, and G. GHERARDI. 1945. The nature and control of reactions in bioluminescence with special reference to the mechanism of reversible and irreversible inhibitions by hydrogen and hydroxyl ions, temperature, pressure, alcohol, urethane and sulfanilamide in bacteria. *J. gen. Physiol.*, 28: 463–537.

——, ——, and R. W. WILLIAMS. 1942. The nature of enzyme inhibitions in bacterial luminescence: sulfanilamide, urethane, temperature and pressure. *J. cell. comp. Physiol.*, 20: 247.

——, and L. SCHNEYER. 1944. The quinine inhibition of bacterial luminescence. *Amer. J. trop. Med.*, 24: 163.

JOHNSON, M. J. 1941. The role of aerobic phosphorylation in the Pasteur effect. *Science*, 94: 200–202.

JOWETT, M. 1938. The action of narcotics on brain respiration. *J. Physiol.*, 92: 322–335.

——, and J. H. QUASTEL. 1937. The effects of narcotics on tissue oxidations. *Biochem. J.*, 31: 565–578.

KALCKAR, H. M. 1941. The nature of energetic coupling in biological synthesis. *Chem. Reviews*, 28: 71–178.

KERR, S. E., and A. ANTAKI. 1938. The carbohydrate metabolism of brain. V. The effect of certain narcotics and convulsant drugs upon the carbohydrate and phosphocreatine content of rabbit brain. *J. biol. Chem.*, 122: 49–52.

KORR, I. M. 1937. Respiratory mechanisms in the unfertilized and fertilized sea urchin egg. A temperature analysis. *J. cell. comp. Physiol.*, 10: 461–485.

——. 1939. Oxidation-reductions in heterogeneous systems. *Cold Spring Harb. Symp. Quant. Biol.*, 7: 74–93.

KRAHL, M. E., and G. H. A. CLOWES. 1936. Studies on cell metabolism and cell division. II. Stimulation of cellular oxidation and reversible inhibition of cell division by dihalo and trihalophenols. *J. gen. Physiol.*, 20: 173–184.

——, and ——. 1938. Physiological effects of nitro- and halo-substituted phenols in relation to extracellular and intracellular hydrogen ion concentration. II. Experiments with Arbacia eggs. *J. cell. comp. Physiol.*, 11: 21–38.

——, and ——. 1940. Studies on cell metabolism and cell division. IV. Combined action of substituted phenols, cyanide, carbon monoxide and other respiratory inhibitors on respiration and cell division. *J. gen. Physiol.*, 23: 413–427.

——, A. K. KELTCH, and G. H. A. CLOWES. 1940. The role of changes in extracellular and intracellular hydrogen ion concentration in the action of local anesthetic bases. *J. Pharmacol. exp. Therap.*, 68: 330–350.

KREBS, H. A. 1943. The intermediary stages in the biological oxidation of carbohydrate. *Adv. Enzymology*, 3: 191–252.

KUMLER, W. D., and T. C. DANIELS. 1943. The relation between chemical structure and bacteriostatic activity of sulfanilamide type compounds. *J. Amer. chem. Soc.*, 65: 2190–2196.

LANGMUIR, I., and V. J. SCHAEFER. 1938. Activities of urease and pepsin monolayers. *J. Amer. chem.* Soc., 60: 1351.

LARDY, H. A., and C. A. ELVEHJEM. 1945. Biological

oxidations and reductions. *Ann. Rev. Biochem.*, 14: 1–28.

——, and P. H. PHILLIPS. 1943. The effect of thyroxine and dinitrophenol on sperm metabolism. *J. biol. Chem.*, 149: 177–182.

LAZAROW, ARNOLD. 1943. The chemical structure of cytoplasm as investigated in Professor Bensley's laboratory during the past ten years. *Biol. Symp.*, 10: 9–26.

LILLIE, R. S. 1916. The theory of anaesthesia. *Biol. Bull.*, 30: 311–366.

LINEWEAVER, H., and D. BURK. 1934. The determination of enzyme dissociation constants. *J. Amer. chem. Soc.*, 56: 658.

LIPMANN, F. 1941. Metabolic generation and utilization of phosphate bond energy. *Adv. Enzymol.*, 1: 99–162.

——, and L. C. TUTTLE. 1945. On the condensation of acetyl phosphate with formate or carbon dioxide in bacterial extracts. *J. biol. Chem.*, 158: 505–519.

MCELROY, W. D. 1943. The application of the theory of absolute reaction rates to the action of narcotics. *J. cell. comp. Physiol.*, 21: 95–116.

——. 1944a. On the specificity of sulfanilamide action. *J. cell. comp. Physiol.*, 23: 109–112.

——. 1944b. The effect of narcotics and other inhibitors on the oxidation and assimilation of glucose by the luminous bacterium *Achromobacter fischeri*. *J. cell. comp. Physiol.*, 23: 171–188.

——, and R. BALLENTINE. 1944. The mechanism of bioluminescence. *Proc. Nat. Acad. Sci. Wash.*, 30: 377.

MEYER, H. H. 1927. Die Narkose und ihre Allgemeine Theorie. In *Handbuch der normalen und pathologischen Physiologie*, A. Bethe, G. V. Bergmann, G. Embden, and A. Ellinger, eds., 1: 531. Julius Springer, Berlin.

MICHAELIS, M., and J. H. QUASTEL. 1941. The site of action of narcotics in respiratory processes. *Biochem. J.*, 35: 518–533.

MITCHELL, H. K., and M. B. HOULAHAN. 1946. *Neurospora*. IV. A temperature-sensitive riboflavinless mutant. *Amer. J. Bot.*, 33: 31–35.

MOULTON, R. F. (ed.). 1939. *Recent Advances in Surface Chemistry and Chemical Physics*. Science Press, Lancaster, Pa.

NEURATH, H., J. P. GREENSTEIN, F. W. PUTNAM, and J. ERICKSON. 1944. The chemistry of protein denaturation. *Chem. Rev.*, 34: 157.

ORMSBEE, R. A., and K. C. FISHER. 1944. The effect of urethane on the consumption of oxygen and the rate of cell division in the ciliate *Tetrahymena geleii*. *J. gen. Physiol.*, 27: 461–468.

OVERTON, E. 1901. *Studien über die Narkose*. G. Fischer, Jena.

PAULING, L. 1946. Molecular architecture and biological reactions. *Chem. engineer. News*, 24: 1375–1377.

PICKETT, M. J., and C. E. CLIFTON. 1941. Effect of selective poisons on utilization of glucose by yeast. *Proc. Soc. exp. biol. N. Y.*, 46: 443–445.

——, and ——. 1943a. On the relations between the oxidation and assimilation of simple substrates by yeast. *J. cell. comp. Physiol.*, 21: 77–94.

——, and ——. 1943b. The effect of selective poisons on the utilization of glucose and intermediate compounds by microorganisms. *J. cell. comp. Physiol.*, 22: 147–165.

QUASTEL, J. H. 1939. Respiration in the central nervous system. *Physiol. Rev.*, 19: 422.

——. 1943. Effects of narcotics and benzedrine on metabolic processes in the central nervous system. *Trans. Faraday Soc.*, 39: 348–359.

RIDEAL, E. K. 1945. Surface chemistry in relation to biology. *Endeavor*, 4: 83–90.

ROBLIN, R. O., JR. 1946. Metabolite antagonists. *Chem. Rev.*, 38: 255–377.

RONZONI, E., and E. EHRENFEST. 1936. The effect of dinitrophenol on the metabolism of frog muscle. *J. biol. Chem.*, 115: 749–767.

SCHMELDES, C., O. WYSS, H. C. MARKS, B. J. LUDWIG, and F. D. STRANDSKOV. 1943. Mechanism of sulfonamide action. I. Acidic dissociation and antibacterial effect. *Proc. Soc. exp. Biol. N. Y.*, 50: 145–148.

SCHULMAN, J. H. 1943. Some physical chemical properties of biologically active molecules. *Trans. Faraday Soc.*, 39: 412–417.

SEVAG, M. G., and M. SHELBURNE. 1942. Cyanide-sensitive bacterial respiratory systems different from the usual cytochrome-cytochrome oxidase system. *J. gen. Physiol.*, 26: 1.

SINGER, T. P. 1945. Enzyme inhibitors and the active groups of proteins. *Brewers Digest*, 20: 85–88, 104–106.

SOSKIN, S., and M. TAUBENHAUS. 1943. Sodium succinate as an antidote for barbiturate poisoning and in the control of the duration of barbiturate anesthesia. *J. Pharmacol. exp. Therap.*, 78: 49.

STANNARD, J. N. 1939a. Separation of the resting and activity oxygen consumption of frog muscle by means of sodium azide. *Amer. J. Physiol.*, 126: 196–213.

——. 1939b. The mechanisms involved in the transfer of oxygen in frog muscle. *Cold Spring Harb. Symp. Quant. Biol.*, 7: 394–405.

——. 1941. Additional evidence of qualitative differences between the resting and activity oxygen consumption of frog muscle. *Amer. J. Physiol.*, 135: 238–248.

STEINBACH, H. B., and F. MOOG. 1945. Localization of adenylpyro-phosphatase in cytoplasmic granules. *J. cell. comp. Physiol.*, 26: 175–183.

STERN, J. R., and K. C. FISHER. 1942. The action of narcotics on the oxygen consumption of frog muscle. *Coll. Net*, 17:

STERN, KURT. 1943. Studies on macromolecular particles endowed with specific biological activity. *Biol. Symp.*, 10: 291–322.

STOTZ, E. 1942. Possibility of a by-pass around the cytochrome system. In *A Symposium on Respiratory Enzymes*, [O. Meyerhoff and others]. Univ. Wisconsin Press, Madison.

——. 1945. Pyruvate metabolism. *Adv. Enzymol.*, 5: 129–159.

STRAUS, O. H., and A. GOLDSTEIN. 1943. Zone behavior of enzymes illustrated by the effect of dissociation constant and dilution on the system of cholinesterase-physostigmine. *J. gen. Physiol.*, 26: 559–585.

SUTER, C. M. 1940. Relationship between structures and bactericidal properties of phenols. *Chem. Rev.*, 28: 269.

TYLER, ALBERT. 1942. Developmental processes and energetics. *Quart. Rev. Biol.*, 17: 197–212, 339–353.

VALKO, E. I. 1946. Surface active agents in biology and medicine. *Ann. N. Y. Acad. Sci.*, 46: 451–478.

VANDENDRIESSCHE, L. 1941. L'action biochimique des dinitrodérivés sur le métabolisme des celles de levure. *Enzymologia*, 10: 69–78.

VAN NIEL, C. B. 1943a. Biochemistry of microorganisms. *Ann. Rev. Biochem.*, 12: 551–586.

——. 1943b. Biochemical problems of the chemoautotrophic bacteria. *Physiol. Rev.*, 23: 338–354.

——, and E. H. ANDERSON. 1941. On the occurrence of fermentative assimilation. *J. cell. comp. Physiol.*, 17: 49–56.

——, and A. L. COHEN. 1942. On the metabolism of *Candida albicans*. *J. cell. comp. Physiol.*, 20: 95–112.

VERWORN, M. 1911. *Narcosis*. (Harvey Lectures). Pp. 52–75.

VOGLER, K. G., and W. W. UMBREIT. 1942. Studies on the metabolism of the autotrophic bacteria. III. The nature of the energy storage material active in the chemosynthetic process. *J. gen. Physiol.*, 26: 157–167.

WARBURG, O. 1914. Über Verbrennung der Oxalsäure an Blutkohle und die Hemmung dieser Reaction durch indifferente Narkotika. *Arch. ges. Physiol.*, 155: 547.

WELCH, A. D. 1945. Interference with biological processes through the use of analogs of essential metabolites. *Physiol. Rev.*, 25: 687–715.

WERKMAN, C. H., and H. G. WOOD. 1942. Heterotrophic assimilation of carbon dioxide. *Adv. Enzymol.*, 2: 135–182.

WINTERSTEIN, H. 1926. *Die Narkose*. Julius Springer, Berlin.

WINZLER, R. J. 1940. The oxidation and assimilation of acetate by bakers yeast. *J. cell. comp. Physiol.*, 15: 343–354.

——. 1943. A comparative study of the effects of cyanide, azide and carbon monoxide on the respiration of bakers yeast. *J. cell. comp. Physiol.*, 21: 229–252.

——, and J. P. BAUMBERGER. 1938. The degradation of energy in the metabolism of yeast cells. *J. cell. comp. Physiol.*, 12: 188–211.

WOODS, D. D. 1940. The relation of p-aminobenzoic acid to the mechanism of action of sulfanilamide. *Brit. J. exp. Path.*, 21: 74.

WYSS, O., V. G. LILLY, and L. H. LEONIAN. 1944. The effect of pH on the availability of para aminobenzoic acid to *Neurospora crassa*. *Science*, 99 18–19.

NEW BIOLOGICAL BOOKS

The aim of this department is to give the reader brief indications of the character, the content, and the value of new books in the various fields of Biology. In addition there will frequently appear one longer critical review of a book of special significance. Authors and publishers of biological books should bear in mind that THE QUARTERLY REVIEW OF BIOLOGY *can notice in this department only such books as come to the office of the editor. The absence of a book, therefore, from the following and subsequent lists only means that we have not received it. All material for notice in this department should be addressed to B. H. Willier, Editor of* THE QUARTERLY REVIEW OF BIOLOGY, *Department of Biology, Homewood Campus, The Johns Hopkins University, Baltimore 18, Maryland, U. S. A.*

REVIEWS AND BRIEF NOTICES

General Biology: Philosophy and Education 59
Biology: History and Biography 61
Ecology 64
Evolution 66
General and Systematic Botany 68
Plant Physiology 71
Economic Botany 72
General and Systematic Zoology 74
Economic Zoology 81
Animal Growth and Development 83
Animal Morphology 85
Animal Physiology 85
Biochemistry 87
Microbiology 92
Health and Disease 93
Psychology and Animal Behavior 96
Human Biology 98
Biometry 102
De Omnibus Rebus et Quibusdem Aliis 103

GENERAL BIOLOGY: PHILOSOPHY AND EDUCATION

DISCOURS DE LA MÉTHODE. *Suivi de Méditations Métaphysiques.*

By René Descartes. Les Éditions Variétés, Montréal. $1.00 (paper). 214 pp. 1946.

This inexpensive new edition of the great classic of scientific method is doubly welcome at the present time, since for the moment, at least, English editions are almost unprocurable. The French style of Descartes deserves special comment. It is as lucid and simple as the precision of his mind. It would be unthinkable to send a novice in the study of German to Kant's *Critique of Pure Reason*, but the clear, limpid French of Descartes should discourage no one who can read that language at all. And what lessons for those who feel that the language of science inevitably requires an esoteric jargon, or who cannot extricate themselves from the repetition of innumerable clichés! The debt modern science owes to Descartes is all too little realized by the rising generations of young scientists, who could be saved much stumbling about in their minds if they but knew more of the "... méthode pour bien conduire sa raison et chercher la vérité dans les sciences."

BENTLEY GLASS

THE COMMON SENSE OF THE EXACT SCIENCES.

By William Kingdon Clifford; edited and with a preface by Karl Pearson; newly edited and with an introduction by James R. Newman; preface by Bertrand Russell. Alfred A. Knopf, New York. $4.00. lxvi + 249 pp. 1946.

This book is already equipped with a preface by Karl Pearson, a second preface by Bertrand Russell that is of value in itself, and an informative introduction of nearly fifty pages by James Newman. It seems redundant to add to this prefatory material. Suffice it to say that biologists especially will welcome this beautifully bound and printed edition of a long unavailable classic because of its intimate connection with Karl Pearson.

Undoubtedly one of the seminal books of the nineteenth century, it belongs alongside of Poincaré's *Foundations* and Karl Pearson's *Grammar of Science*. Although more limited in scope than either, it cuts every whit as deep. It should be added that Clifford's is an extremely sophisticated and mathematical type of common sense.

GAIRDNER MOMENT

BIOLOGIA. *Volume 1, Number 1. Pp. 1–4. January, 1947.*

Frans Verdoorn, editor. Published as a supplement to Chronica Botanica, Waltham, Massachusetts. Subscriptions to *Biologia* only, $4.00 for two years, one volume with index.

Biologia is to be the Official Bulletin of the principal international biological societies, commissions, and congresses. It is to be kept small and informal, and will be restricted to news. It will not publish articles or discussions. Its format is that of a four-page leaflet, 15″ x 9″, printed in triple columns. It is an encouraging sign of the reawakening life of international science.

LE MICROSCOPE: *Emploi et Applications. Volume I. Encyclopédie Pratique du Naturaliste, XXXIII.*

By E. Séguy. Paul Lechevalier, Paris. 267 fr. cccxx + 126 pp. + 102 plates. 1942.

This addition to a series of French popular works on biology appears to be only the first of two volumes on practical microscopy. Written by E. Séguy, the well-known entomologist of the Muséum National d'Histoire Naturelle, it is obviously intended for the amateur microscopist rather than the professional biologist. The text consists of 771 numbered paragraphs dealing with the history of microscopy, optical systems and principles, reagents, fixatives and stains, methods of making temporary and permanent microscopical preparations, vital staining, microdissection, embedding and section-cutting (to mention only a few of the topics touched on). Many little-known but interesting special methods are described in these sections; much space is devoted to descriptions of unusual optical systems, but some of the basic concepts of microscopy, such as numerical aperture, receive over-brief treatment. The text is followed by plates, which illustrate the microscopes manufactured by only three firms (Zeiss, Nachet, and Vion), together with a miscellany of 'microscopic objects' (planktonic organisms, protozoa, molluscan radulae, fleas, fish-scales, bryozoa, etc.) likely to be studied by one to whom microscopy is a hobby rather than a method of serious scientific investigation.

M. J. D. WHITE

GENERAL BIOLOGY. *Third Edition.*

By William C. Beaver. The C. V. Mosby Company, St. Louis. $4.75. 820 pp. + 14 plates. 1946.

The general plan of presentation of the earlier editions has been essentially maintained in the present edition of this excellent standard college textbook. New materials have been added to bring the work up to date with respect to penicillin, viruses, and human biology.

Part I introduces the student to the general principles and concepts of biology and presents materials on the properties of living matter, the activities of the cell and its relationship to the whole organism, and the structure and function of the tissues, organs, and systems of animals and plants.

The field of animal biology is covered in Part II. A brief presentation of the 12 phyla and a summary of the number of species of animals is followed by a comprehensive discussion of the comparative anatomy and physiology of the organ systems of 19 representative animals. A short chapter on embryology, a thorough presentation of the biology of man, and a discussion of the economic importance of animals conclude this section.

In Part III, the biology of plants is presented in a manner quite similar to that for the animal kingdom in Part II. A survey of the 4 phyla of plants prepares the student for a study of the comparative structure and function of the systems of 9 common plants. Part III is concluded with a chapter on the economic value of various members of the floral world.

The final section (Part IV) is devoted to authoritative discussions on the history of biology, ecology, genetics, evolution, and applied biology.

Each chapter of the text is concluded with a list of questions and topics for discussion on the material presented therein. The work is beautifully illustrated, and carries appendices on (1) important prefixes and suffixes used in biology, and (2) a glossary of biological terms. There is a table of contents and a complete index.

The present edition of this fine work will undoubtedly maintain the popular place in the college classroom which was achieved by the earlier editions.

B. AUBREY SCHNEIDER

SCIENCE ALL ABOUT US. *Our World of Science.*

By Gerald S. Craig and Agnes Burke. Illustrated by David Hendrickson, Jacob B. Abbott, and Harold Sichel. Ginn and Company, Boston. $1.04. 160 pp. 1946.

The contents of this book are far less formidable than the title implies. Excellent colored illustrations combined on every page with a few simple sentences make a book that children who are learning to read will surely enjoy. Such subjects as the magnets, the seasons, weather, plants, animals, and what makes things go are considered from the view of the everyday experience of children.

J. CUSHING

EXPLORING OUR WORLD. *New Edition. Adventuring in Science.*

By Samuel Ralph Powers, Elsie Flint Neuner, Herbert Bascom Bruner, and John Hodgdon Bradley. Ginn

and Company, Boston. $1.64. viii + 522 pp.; 1 plate. 1946.

One must refer to the publisher's pamphlet to find out that this newly revised textbook is planned for the first year of the Junior High School (7th grade). The "exploration" involves six units: Science in Our Lives; The World of Water; The World of Air; The World of Rock; The World of Living Creatures; The World of Action. In all of these, and not in the fifth unit alone, there is excellent integration of biological and physical studies. An entirely new chapter, How Does Man Fit into the Web of Life?, has been added to the fifth unit. This takes up the relation of man to his environment, his community existence, and his responsibility as a scientific creature today and in the future. Each chapter is interspersed with exercises, and at the end of each there is a list of erroneous statements to be corrected, of questions for discussion, and of things to do. There is some emphasis on experiment, but in general the approach is descriptive. Illustrations, both drawings and photographs, are abundant and excellent. The style is simple and direct, if a bit choppy. There is a workbook to accompany the text and also a teacher's manual. As a whole, the book leaves little doubt that it will stimulate interest in science among young students and provide a good introduction to further work. It does not represent an attempt to survey the fields of physical and biological science on a comprehensive scale, so that after a series of such books has been used, the youth's knowledge may present considerable gaps of a sometimes surprising nature and order.

BENTLEY GLASS

BIOLOGY: HISTORY AND BIOGRAPHY

HISTOIRE DES SCIENCES ET DE LEURS APPLICATIONS. *By Louis Bourgoin. Éditions de l'Arbre, Montréal.* $1.50 (paper). 327 pp. 1945.

Like all too many books published in English, this volume bears a title several sizes too big for it. In no sense is it a connected history of science, nor an outline of the ideas and discoveries of major importance. That it is not really intended to be either can be seen from the table of contents, which includes, inter alia: metals known to the ancients; methods of measuring time; the alchemy of the Arabs; theories of matter from Cleopatra to Marie Curie; Roger Bacon and his times; Boyle; Galileo; the three discoverers of oxygen; Denis Papin. Little after 1800 is included.

Within these limits the book is an admirable series of semi-popular essays, clear, informative, and fair. Some might suspect an "arrière-pensée" in the author's insistence that science cannot be created by proud reason alone. But did not the great Poincaré himself fail in his attempt to uncover the methods by which scientific discoveries are made? It would be a bold man, and an unscientific one, who became dogmatic on this point.

GAIRDNER MOMENT

LUTHER BURBANK: *A Victim of Hero Worship. Chronica Botanica, Volume 9, Number 5/6. By Walter L. Howard. The Chronica Botanica Company, Waltham, Massachusetts; G. E. Stechert and Company, New York.* $3.75 (paper). Pp. 299–508 + 7 plates. 1945.

This scholarly and historically accurate analysis of the life and work of Luther Burbank, by Walter L. Howard, one of the country's leading horticulturists, is an intriguing book. It was written in a spirit of fair play, to enable the reader better to understand and appreciate the real Burbank, admittedly a difficult task. Few prominent men have been so actively praised and condemned at one and the same time. There was no half-way ground; a person believed in Burbank or he didn't. To his host of admirers he was a great "benefactor, a knight in shining armor"; to his enemies he was an unscrupulous charlatan or worse. Burbank's temperament and eccentricities and the unorthodox nature of his work helped to cloud the issue and aided the long and bitter controversy which raged while he was alive and which has persisted after his death.

The present work is not a conventional biography, but a series of character sketches, prepared in an attempt to study Burbank's career objectively and to explain and clarify some of the principal controversial episodes of his life. The author strives to break through the maze of conflicting versions and find the truth. Whether or not the reader will come to the author's conclusion that the real Burbank was "every inch a man of worth, a man of original ideas, a man with a definite mission in life, fully capable of standing on his own feet as a lone worker in the field of science" will probably depend to a great extent on his own interpretation of the data presented. It might be well for him to bear in mind that the author's purpose in telling the story was not to "debunk" Burbank, or his critics either, but merely to state what "appears to be the truth." The book will not please the extremists in either camp, but the people who have no strong feelings either way will find set down, often for the first time, the evidence about the man and his work, his value to society, and to the science of plant breeding. After reading it, they will be better able to draw their own conclusions.

The author first paints the general background and then presents a series of chapters dealing with Burbank the Man, the Nurseryman, the Scientist, the Egoist,

the Mentor of Youth, the Pariah – of Scientists, the Disappointed, the World Character, the Individualist. These are followed by similar discussions of Burbank's ethics, religion, foray into Science (the Carnegie Grant), admirers, detractors, and place in the Hall of Fame.

The book concludes with a summary of Burbank's productions, taken from the author's more technical report, *Luther Burbank's Plant Contributions* (Bull. 691. Calif. Agric. Exp. Sta.), a statement of the present status of Burbank's plant breeding experiments, and a brief genealogical account of the Burbank family.

ALBERT F. HILL

A HISTORY OF MEDICINE.

By Douglas Guthrie, with an introduction by Samuel C. Harvey. J. B. Lippincott Company, Philadelphia, London, and Montreal. $6.00. xvi + 448 pp. + 72 plates. 1946.

In 400 pages the author has tried to give us the history of medicine between 15,000 B. C. and the beginning of this century. That this is no easy undertaking is clear. Such an attempt to write a one-volume history of medicine can probably only be successful, if at all, under two conditions: the author must either be a brilliant writer, or he must have a new and original approach to the whole problem. Both these qualities are absent from the present book. In a somewhat pedestrian manner oft-told stories are repeated, most of them obviously taken from second-hand sources. The number of errors, unavoidable in such an undertaking, is relatively small; but for reference purposes the book is too short, and it may be doubted whether it can make any new friends even for such an attractive subject as the history of medicine.

ERWIN H. ACKERKNECHT

WILLIAM BEAUMONT'S FORMATIVE YEARS: *Two Early Notebooks 1811–1821.*

With annotations and an introductory essay by Genevieve Miller. Henry Schuman, New York. $6.00. xvi + 87 pp. + 21 plates. 1946.

The observations of William Beaumont, the backwoods surgeon, on the gastric fistula of Alexis St. Martin (published in Plattsburg, New York, in 1833) are one of the lasting glories of American medicine. Two notebooks, one medical and one non-medical, which Beaumont composed between 1811 and 1821, give interesting glimpses into the professional background and character of our medical hero and his times. Genevieve Miller has very competently annotated these notebooks, tracing the numerous names and quotations which they contain. Publisher and printer have taken great care to produce a very handsome little volume.

ERWIN H. ACKERKNECHT

NEW ASPECTS OF JOHN AND WILLIAM HUNTER. *I. Everard Home and the Destruction of the John Hunter Manuscripts. II. William Hunter and His Contemporaries.*

By Jane M. Oppenheimer, with a foreword by Fenwick Beekman. Henry Schuman, New York. $6.00. xx + 188 pp. + 5 plates. 1946.

The characters of great men tend to be stereotyped by the passage of time and the repetitions of historians. This is especially the case with scientific and medical men, who are often written about by enthusiasts who depend exclusively upon secondary sources. Such a process has certainly modified the general memory of the personalities who built a world center of biological science at the Great Windmill Street School of Anatomy in London in the last third of the eighteenth century. William Hunter, the obstetrician-anatomist, a fastidious patron of science; John Hunter, the hypertensive, irascible investigator and collector; Sir Everard Home, the unfaithful scientific executor of his brother-in-law John, plagiarist and destroyer of records; William Clift, a neglected and accusing Man Friday,—these are the images that time is leaving us, in far too low relief, of these four men of science.

Jane Oppenheimer now comes forward, with evidence gathered from contemporary records, to redelineate the characters of Everard Home and William Hunter. The result of her studies is to exculpate Home, at least partially, of the most serious charges against him. His friends, as well as his enemies, of course deplored his act in burning the unpublished scientific papers of John Hunter, if only because it laid him open to the worst suspicions. Jane Oppenheimer shows, however, that in his papers written after Hunter's death, and allegedly plagiarized from the records later destroyed, Home made unequivocal acknowledgment of his indebtedness to Hunter. Home's frankness in telling about his destruction of the papers, at a time when the co-executor, Matthew Baillie, was still living, and William Clift was in a position to call down blame upon Home, shows that the latter did not consider his action a faulty one. Finally, Miss Oppenheimer points out that Clift's relations with John Hunter and with Home must have made him jealous of the former's honor and envious of the latter as a successful surgeon and teacher. He may well have been over-suspicious of Sir Everard. Home's own defense was that Hunter wished the papers to be destroyed, because they were incomplete and not adapted to publication. The author seems inclined to accept this as somewhere near the truth of the matter.

The second essay is devoted to William Hunter, with

the aim of bringing him out from the shadow of his celebrated brother and of depicting his personal qualities and character. Readers of medical history know something of his services in making obstetrics a dignified specialty and in elevating the quality of the teaching of anatomy. They will be less prepared for this account of his tactics as a social climber in the profession, which were successful enough to make him obstetrician to Queen Charlotte, and which at a later period led him to desert the liberal cause and join the King's party. That his mind was complex and devious in small affairs as well as great, and that a good deal of self-seeking was intermingled with his devotion to science, is amply proved by this essay.

The book is lucidly written and well documented, with notes and bibliographies and a list of Sir Everard Home's publications. The format is attractive.

GEORGE W. CORNER

DAVID RITTENHOUSE: *Astronomer-Patriot, 1732–1796. Pennsylvania Lives.*

By Edward Ford. University of Pennsylvania Press, Philadelphia. $2.50. viii + 226 pp. + 1 plate. 1946.

David Rittenhouse was probably the greatest scientific genius that this country has produced, yet it is the irony of fate that most of those to whom his name is familiar think of him only as the man for whom a square, a street, and a club have been named.

There is nothing in his ancestry to indicate the origin of his scientific interests. His mother was a woman of no education whatever, and as she was an adopted child, little is known of her forebears. His paternal ancestry can be traced no further than his great-grandfather William, by birth a German of Swiss descent, who settled in Amsterdam and became a Dutch citizen.

In those days the German population of America consisted largely of sects of Anabaptist origin which had settled in Pennsylvania at the invitation of William Penn to escape the religious persecutions that were beginning to develop in Germany. Although William Rittenhouse was an ordained minister of the Mennonite church, his immigration was actuated not by religious but by commercial motives. He was an expert paper-maker and there were no paper mills in the colonies. Early in the eighteenth century, accompanied by his wife and two sons, he arrived in New York, but before he could establish himself industrially the Mennonite migration into Pennsylvania had begun, the first ship-load of settlers to arrive erected a church in Germantown, and to it they called William Rittenhouse to be their first pastor. Thus the Rittenhouse family became established in Pennsylvania.

The site selected for their paper mill was in the bottom of a deep canyon where there was an abundance of water power, but access to it was difficult, and its extreme dampness was not conducive to bodily health. When David's two older brothers died, and he himself had developed a chronic weakness that is now believed to have been caused by ulcers of the stomach, his father Matthias withdrew from the mill and settled on a farm near the modern village of Fairview Four Corners.

Matthias was not a farmer, and he learned farming the hard way by trial and error, but eventually he succeeded in making a success of his occupation. Although David tried to please his father by working on the farm, he took little interest in the work. His uncle David Williams, for whom he was named, was one of the few Americans to possess a copy of Newton's *Principia*, and when he died and left his library and chest of tools to young David, the youth's career was settled. He began with the construction of mechanical models and then turned to the manufacture of clocks.

The neighbors looked askance at this farmer's boy who had never served as an apprentice to a clock-maker, and when he began to study astronomy in order to make his clocks keep better time, the contemporary horologists eyed him in the same way. He was by no means the first clock-maker in the colonies, but he was the only self-taught one, and none of the others could do better work. His most famous clock is the one formerly owned by George W. Childs. It shows the day of the month and the month of the year, as well as the phases of the moon and the equation of time, and has ten sets of chimes.

From the manufacture of clocks it was a short step to that of astronomical instruments. When the transit of Venus occurred in 1769, the American Philosophical Society sent out three different expeditions to observe it. As the final contact was not visible in Europe, the Royal Observatory lent some of its equipment for use in America, but most of the equipment came from the Rittenhouse workshop. An interesting detail of construction was the use of spider webbing for telescope sights. These delicate filaments had been previously used by an Italian astronomer, but Rittenhouse seems to have discovered their advantages independently. The observations of the transit were successful and made possible the computation of the distance between the earth and the sun to a degree of accuracy previously unobtainable.

Rittenhouse's masterpieces were his two orreries. These were mechanical models that reproduced the motion of all the planets and satellites known at the time. Unfortunately this biography by Ford is not adequately illustrated, and there is nothing to give the reader any idea of what these remarkable contrivances were like. In addition to them, Rittenhouse also constructed a machine for forecasting eclipses.

In addition to his astronomical work, Rittenhouse played a large part in establishing the boundary lines of

the colonies. Pennsylvania employed him to mark the line dividing that state from Virginia, the Western Reserve, and New York. New York also employed him to run the lines on the New Jersey and Massachusetts borders. He also checked the boundaries of Delaware and Maryland. Later he laid out the course of the Philadelphia and Lancaster Turnpike, the first in the United States, and made the surveys for the canals along the Delaware, Schuylkill, Lehigh, and Susquehanna rivers. How he ever found time for political activities defies the imagination, yet he served several terms in the Pennsylvania Assembly, and was also director of the State Loan Office, and later of the Mint.

In the pages of this book we meet with many of the important personages of our national history. In addition to Franklin, Washington, Adams, and Jefferson, all of whom were intimate friends of David Rittenhouse, we come across William Henry and John Fitch, who built and operated steamboats in 1763 and 1785, respectively; Francis Hopkinson, America's first song writer; "Baron" Stiegel, the glass-blower of Mannheim; André Michaux, the botanist who explored so many remote corners of four continents in the eighteenth century; Thomas Priestley, the discoverer of oxygen; Adam Kuhn, the only American to study under Linnaeus; William Cobbett, better known under the pseudonym of "Peter Porcupine"; and the Rev. William Smith, whose loyalty to the king compelled him to leave the colony during the Revolution (this man must not be confused with another William Smith who was one of the Virginia exiles).

Ford reminds us that a comparison between Franklin and Rittenhouse is inevitable. The difference is that Franklin was an inventor rather than a scientist. The phrase "for the Promotion of Useful Knowledge" occurs in the names of both scientific societies which he founded. On the other hand, Rittenhouse was interested in the pursuit of Truth, whithersoever he might be led. When he invented the diffraction grating he seems to have had no idea that it would someday serve a useful purpose in his favorite science of astronomy. No subject was unworthy of his attention, and we find him investigating the compressibility of water, the ability of the rattlesnake to charm its prey, the contraction and expansion of wood with changes of temperature, and the reproductive process of the opossum. According to the author, he was a great reader, his favorite writers being Bunyan, Milton, Pascal, and Lessing, of one of whose plays he made an English translation. His interests were much more diverse than those of Franklin.

His final illness was painful but mercifully brief. Death came quickly and the reader is likely to feel that it must have been like that of the astronomer in the poem whose last words were

"Though my soul shall set in darkness it will rise in perfect light,
I have loved the stars too truly to be fearful of the night."

ECOLOGY

FOREST SOILS AND FOREST GROWTH. *A New Series of Plant Science Books, Volume XVIII.* *By S. A. Wilde. The Chronica Botanica Company, Waltham, Massachusetts; G. E. Stechert and Company, New York.* $5.00. xxii + 242 pp. 1946.

The first book in this country to show the relationship between forest cover and soils was Hilgard's *Soils*, published in 1906. The second is Wilde's *Forest Soils and Forest Growth*, which is at the same time the first book in the English language, so far as is known to this reviewer, devoted wholly to forest soils. In this country, soil scientists and foresters have been active in their respective fields since early in the present century, but it has been only in the last 15 years or so that forest soils have been made the subject of research as an adjunct to forest management. Previously such research was chiefly a phase of genetic soil studies concerned with soil development. From cover to cover, Wilde centers the discussion in the forest,—the relation of the soil in all its ramifications to forest composition, growth, vigor and health, and use, although he makes frequent reference to agricultural soils for comparison.

Following a brief but satisfactory historical introduction, there are three chapters on forest soil genesis and the genetic soil groups of the world, and one each on forest cover, physical properties, chemical properties, soil organisms, forest humus, soil-forest types, forest soil survey, silvicultural cuttings in relation to soils, productivity of forest soil, and five chapters on nursery soils and their management.

Wilde's first-hand familiarity with both eastern and western European conditions and his knowledge of the languages of those regions make him preeminently fitted to bring together a wealth of material from that part of the world, in a form readily assimilated by the American student. At the same time, however, one has the feeling that the author has drawn a bit too freely upon foreign material, and has cited too many examples of foreign conditions and experiences. Such a situation is inevitable considering the greater backlog of experience abroad.

Objection is likely to be raised to the use of such terms as "melanized" (humus-incorporated) soils; "grood" (prairie-forest) soils; "charral" soils (those supporting sclerophyllous forests); "bor" sands (weakly podzolized sandy soils); "taiga" forest (conifers on podzol soil), and "near-taiga" (mixed hardwoods and conifers on podzolic soils); "allite" and "siallite" (a soil rich in aluminum and poor in silica, and one containing

aluminum and silica in about equal proportions, respectively). Whether or not they will find a permanent place in American soils' literature remains to be seen.

Wilde's classification of forest humus is considerably simplified from that of Heiberg and Chandler, and differs from the latter in that it recognizes the complex type "duff mull" as a main type. Duff mull corresponds most nearly to Heiberg and Chandler's "twin mull." It is doubtful if this classification would be adequate for the Northeast; but it is also doubtful if there ever will be a classification that will fit all conditions and satisfy everyone, at least not until it can be built upon a firmer footing than it is now. In the absence of rather definite measurable characteristics in the field, differences of opinion can be expected.

The seriousness of uncontrolled forest fires and the rather common practice of controlled burning would seem to warrant a fuller discussion of this important subject than this book contains. Probably this defect will be corrected in subsequent editions.

The book is written in a clear, moderately technical style, and is not difficult reading. Good use is made of sketches, and the plates are well chosen. The printed volume is a vast improvement in appearance and legibility over the two previous mimeographed editions, and includes a number of important changes in content and arrangement. Originally intended for use by "a rather heterogeneous group of students, including graduates and upperclassmen in soils, forestry, botany, game management, and landscape architecture," the book in its present form should prove equally useful to practising foresters, ecologists, nurserymen, and soil conservationists.

HERBERT A. LUNT

THE BOBWHITE QUAIL: *Its Habits, Preservation, and Increase.*

By Herbert L. Stoddard. Charles Scribner's Sons, New York. $6.00. xxx + 559 pp. + 69 plates. 1946.

Leopold has outlined the sequence of ideas in game management as follows: First, restriction of hunting; second, predator control; third, reservation of game lands; fourth, artificial restocking and game farming; and fifth, manipulation of the environment (Game Management, *Scribner's*, 1933: 5). In 1931, when *The Bobwhite Quail* was first published, game management in this country was in the fourth stage. A few conservationists were beginning to visualize the fifth stage, often, however, only in relation to the welfare of "planted" stock. A very few had come to realize that game management is *primarily* management of the environment. *The Bobwhite Quail* is the record of the first full-scale attempt to manage a North American game bird according to this principle.

The book is based on five years of field work on the life history and management of bobwhites in the southeastern states. The material on life history is given in the first thirteen chapters, and includes: types of quail range; mating, nesting, rearing of young, covey formation and behavior; growth, plumages, sex ratio; foods and feeding habits (by C. O. Handley and Clarence Cottam); internal parasites (by Eloise B. Cram, Myrna F. Jones, and Ena A. Allen); external parasites, non-parasitic diseases, and other mortality factors; movements, as shown by banding; population fluctuations; and the influence of agricultural practices. Three examples will give an indication of the quality of the data: the analysis of nesting habits is based on the study of 602 nests, which were visited 2,160 times; the sex ratio is based on 40,000 individuals; approximately 2,400 birds were banded in the study of movements.

Seven chapters on quail management are founded upon this life history material. They discuss general procedures for building up food supplies and cover, as a part of preserve management (by Stoddard and Handley); the use of fire; predator control; methods of capturing quail; artificial propagation (by W. B. Coleman and Stoddard); and the use of "Mexican" quail in restocking. It is worth emphasizing that these management procedures were derived from field study of methods already in use, and from field testing of new techniques; they are the result of what Grange has called "dirt" management in contrast to "paper" management (*Trans. 18th Amer. Game Conf.*, 1931: 56).

The book is handsomely made. Photographs and line drawings, and four color plates by E. R. Kalmbach, add greatly to its usefulness.

The Southeast has changed since 1931. Quail management has been modified by changes in the economic structure and the farming practices of the region, and by a changed attitude toward indiscriminate woods burning. Stoddard and a number of others have published on some of these modifications, and on some wholly new information, but their papers are scattered through the literature. It is disappointing that *The Bobwhite Quail* was not revised, instead of being merely reprinted. However, the recent material only supplements, and in no sense replaces, Stoddard's original work.

In short, *The Bobwhite Quail* is both the oldest comprehensive treatise on the management of an American game bird, and the basic modern handbook for its region. And it is much more. For fifteen years it has been a model for studies in game-bird management, and an inspiration to authors. After fifteen years, it is still the standard of excellence for such studies. It has not yet been surpassed.

F. N. HAMERSTROM, JR.

ANNALES BIOLOGIQUES, *Volume I, 1939–41. Conseil Permanent International pour l'Exploration de la Mer. Edited by H. Blegvad. Andr. Fred. Høst et Fils, Copenhagen.* Kr. 10.00 (paper). 190 pp. + 1 chart. 1943.

It is to be hoped that this will be the first of a series of annual or periodical analyses of the fluctuations of populations of marine fishes in the North Sea and Northern Atlantic, which have been part of the work of the International Council. The war prevented organization of this phase of the Council's activities in 1939, and it was not until 1943 that the material ready at that time could be published. The principal fishes discussed in this first volume are the herring, cod, plaice, and sprat. There are also papers on other fish and an article on the effect of whaling on the Antarctic Stock. This first volume is edited by H. Blegvad with an introduction by Johan Hjort.

J. W. HEDGPETH

OCEAN ATMOSPHERIC-ELECTRIC RESULTS. *Scientific Results of Cruise VII of the Carnegie during 1928–1929 under Command of Captain J. P. Ault. Oceanography—III. Department of Terrestrial Magnetism, Carnegie Institution of Washington Publication 568. By O. W. Torreson, O. H. Gish, W. C. Parkinson, and G. R. Wait. Carnegie Institution of Washington, Washington.* $2.75 (cloth); $2.25 (paper). viii + 178 pp. 1946.

This volume of the Carnegie reports contains the usual complete description of the methods and instruments employed, and a full tabulation of the data gathered with continuous recording apparatus during the Carnegie's last cruise. Measurements were made of positive and negative conductivity, ionic density, radiation, radioactive content of air at sea, and the number of condensation nuclei.

EVOLUTION

L'ORIGINE DES ESPÈCES. *"Que Sais-Je?" Le Point des Connaissances Actuelles. By Émile Guyénot. Presses Universitaires de France, Paris.* 15 fr. (paper). 128 pp.; ill. 1944.

It is truly illuminating to see how much of the modern knowledge of evolutionary processes can be treated, and treated well, within such narrow limits of space. Guyénot has followed the development of the genetic theories on which neo-Darwinism is now firmly based, and perhaps no one now living has a greater grasp than he of the history of the theory of evolution. The result is a compact little book that is excellent in many respects. Its defects appear to stem from the isolation of the European scientists during the war years, so that Guyénot was not, at the time of writing, familiar with the outstanding contributions made to the study of evolution, during the war period, by such English-speaking authors as Mayr, Huxley, and Simpson, or, indeed, even the earlier works of Dobzhansky and Goldschmidt. The result markedly weakens the conclusions Guyénot reaches, and leaves him open to an unwarranted pessimism as to our ability to ascertain the real factors of evolution and their relative importance.

Guyénot's analysis of paleontology and its bearing on the character of evolution seems particularly weak and in need of revision. He places strong emphasis on the discontinuity of the record, on the irreversibility of evolution, and on orthogenesis as an inexplicable and inherent force. He excludes *Archeopteryx* from the ancestry of modern birds, and *Pithecanthropus* and *Sinanthropus* from that of man. These views have led Guyénot to a conclusion even more radical than that of Goldschmidt, namely, that the little fluctuations in all directions, upon which Darwin laid such stress, "which constitute individual variability and which besides are the consequence of variations of the surroundings, are not hereditary, and have, then, no evolutionary value" (p. 60). This is to ignore the fact that the effects of mutations are not always large, and that the slight variations are by no means always the result of environmental action, but may well be genetic and consequently of very great evolutionary importance. Yet not even the most extreme mutations observed have ever, thinks Guyénot, given rise to a new organ. "Mutations are the daughters of chance. But how can there emerge, from a series of chances, the acquisition of a new organ with the innumerable connections which its functioning requires?" (p. 124). Having earlier denied the evolutionary value of small variations, and now recoiling from the idea of macromutation, Guyénot is forced to fall back on Bergsonian philosophy, and concludes dismally: "... there must intervene some modification of unknown nature.... Of variations of this kind, we have not a single example; it is impossible for us to imagine them. In this sense, the great steps of evolution escape us entirely." (p. 126). This was not the point of view that appeared to be generally accepted by those who attended the Princeton Bicentennial Conference on Genetics, Paleontology, and Evolution in January of this year.

BENTLEY GLASS

CATALOG OF THE EGAN COLLECTION OF SILURIAN INVERTEBRATE FOSSILS *at The Chicago Academy of Sciences. Special Publication Number 7. By John R. Ball and Katherine F. Greacen. The Chicago Academy of Sciences, Chicago.* 50 cents (paper). 55 pp. + 1 plate. 1946.

The fossil invertebrate collections of The Chicago Academy of Sciences are known as the "W. C. Egan Collection" in honor of the late Chicago amateur scientist whose private collection forms the major part of that assemblage. The present catalogue of the Silurian fossils, although it considers only a part of the whole collection, is of particular value, since strata of Silurian age are extensively developed in the Chicago area and the faunas from these rocks are unusually well-represented in the Academy's collection. The present report gives bibliographic, locality, and museum catalogue data for 263 species. Sixteen species are represented by type material of various category; these are separately listed with pertinent additional information. A short bibliographical sketch and portrait of W. C. Egan is included.

INTRASPECIFIC VARIATION IN, AND ONTOGENY OF, PRIONOTROPIS WOOLLGARI AND PRIONOCYCLUS WYOMINGENSIS. *Bulletin of the American Museum of Natural History, Volume 86, Article 4.*

By Otto Haas. American Museum of Natural History, New York. $1.85 (paper). Pp. 141–224 + 14 plates. 1946.

Prionotropis woollgari Meek and *Prionocyclus wyomingensis* Meek are ammonites of Upper Cretaceous age. Each species is a guide fossil of a faunal zone in the Carlile shale and equivalent rocks of the western United States.

An examination of 450 specimens of *Prionotropis woollgari* and 40 specimens of *Prionocyclus wyomingensis* reveals a high degree of intraspecific variation and ontogenetic changes in both of the species. The *forma typica* of each of the species is defined. Six varieties of *Prionotropis woollgari* and two varieties of *Prionocyclus wyomingensis* are described and illustrated. The ontogenies of the *forma typica* and varieties of each species are closely characterized with respect to the dimensions, estimate of full size, whorl section, ornamentation, and suture lines. This study shows that intraspecific variation of these species is largely due to differentiation in speed of development. Sculptural ontogeny shows the appearance, further development, vanishing, and eventual disappearance of the elements of ornamentation, and a general trend toward diminishing fineness and density of these elements. Sutural ontogeny shows the first lateral lobe to change from trifid to bifid.

The generic differences between *Prionotropis* and *Prionocyclus* are discussed. Particular attention is given to the serration of the keel, dominance of the tubercles in the mature ontogenetic stages, presence or absence of secondary ribs, and the degree of incisiveness of the suture. The variety *praecox* of *Prionotropis woollgari* is transitional between the genera.

Homeomorphies between the earlier Cretaceous ammonite genus *Pervinquieria* and *Prionotropis* and *Prionocyclus* are pointed out and illustrated by several examples. Certain generic differences are noted.

W. A. COBBAN

THE GENERA OF FOSSIL CONCHOSTRACA—AN ORDER OF BIVALVED CRUSTACEA. *Bulletin of the Museum of Comparative Zoölogy at Harvard College, Volume 96, Number 3.*

By Percy E. Raymond. Museum of Comparative Zoölogy, Cambridge, Massachusetts. $2.00 (paper). Pp. 215–307 + 6 plates. 1946.

This short preliminary monographic report is well summarized by the author in his Introduction: "My efforts . . . have been confined to an attempt to describe the characteristics of the genera, and to list under them their various species. The study has necessarily been largely from the literature and is subject to revision . . . . My chief purpose in publishing this article at the present time is to point out that what paleontologists have called Estheria is not an Estheria, and that there are several easily recognizable genera in the complex which has passed under that name."

Two new families, fourteen new genera, and thirty-eight new species are described.

PAREIASAURS VERSUS PLACODONTS AS NEAR ANCESTORS TO THE TURTLES. *Bulletin of the American Museum of Natural History, Volume 86, Article 6.*

By William King Gregory. American Museum of Natural History, New York. 75 cents (paper). Pp. 275–326 + 2 plates. 1946.

Two opposed and classical views have derived the turtles (Chelonia) from the specialized and aquatic plesiosaurs on one hand, and from the primitive cotylosaurs on the other. The case has been reopened and the data reexamined by the author, whose conclusions strongly favor the descent of the turtles from the Cotylosauria. Such an affinity was first suggested by Cope in 1880, and has been supported since by Williston, Watson, Hay, and von Huene. Gregory indicates that the Chelonia were derived in the upper Pennsylvanian or lower Permian from the pareiasaur branch of the Cotylosaurs. This group, although large in size, had considerable dermal armor on skull, back, and sides and showed dental characteristics that might have developed into the toothless, horny beak of turtles. Most authorities agree that the most primitive living turtles are the terrestrial tortoises, which presumably resembled somewhat the first chelonians. The author has given a detailed comparison of turtle skeletons,

living and fossil, and those of diadectid, pareiasaur, captorhinomorph, seymouriamorph, and placodont reptiles.

HYPSOGNATHUS, A TRIASSIC REPTILE FROM NEW JERSEY. *Bulletin of the American Museum of Natural History, Volume 86, Article 5.*

By Edwin Harris Colbert. American Museum of Natural History, New York. 95 cents (paper). Pp. 225–274 + 9 plates. 1946.

Much interest has been manifested in the so-called "stem-reptiles" or Cotylosauria since their discovery by Cope in the Texas Permian. This paper concerns one family, the Procolophonidae, and in particular the genus *Hypsognathus*. The very well preserved remains of *Hypsognathus fenneri* discussed by Colbert are from the upper Triassic of New Jersey. He reviews the morphology, phylogenetic position, and geological range of the Procolophonidae. The earliest records of the group are from the upper Permian of Russia and South Africa, and the later remains from the lower (Europe, South Africa), middle (Scotland), and upper Triassic (North America) indicate an eventual cosmopolitan range. *Hypsognathus* is a late and specialized member of the family, although small in size, and is likened by the author to the North American horned lizard *Phrynosoma* in appearance and ecological relations. The procolophonids are the last of the interesting and diversified Cotylosauria, from which sprang the mammal-like reptiles and eventually the mammals. Colbert's scholarly work is a welcome addition to our knowledge of this important group of reptiles.

NOTES ON PLEISTOCENE AND RECENT TAPIRS. *Bulletin of the American Museum of Natural History, Volume 86, Article 2.*

By George Gaylord Simpson. American Museum of Natural History, New York. 75 cents (paper). Pp. 33–82 + 6 plates. 1945.

This paper concerns chiefly the description of the almost complete skeleton of a new species of Pleistocene tapir, *Tapirus excelsus*. The author also has reviewed taxonomically those species of the North American Pleistocene of which there is the most abundant material (*Tapirus veroensis, tennesseae, haysii,* and *copei*). He has examined in considerable detail the skeleton, especially the skull and teeth, of the recent South American species, *Tapirus terrestris*. These data have been treated statistically, and have served as the basis for comparison of the living forms and the Pleistocene types of North America. The three groups of living tapirs (Central American, South American, and Indian) have been combined by Simpson with the Pleistocene forms in a single genus *Tapirus*. He has noted that the fossil remains are from points south of the spread of the continental glaciers, and within the present area having a minimal annual rainfall of 20 inches. That tapirs were living in this region of the United States when man entered North America is supported by finds in Arizona, Oklahoma, and Florida.

GENERAL AND SYSTEMATIC BOTANY

THE STUDY OF PLANTS: *A Laboratory-Discussion Manual of Botany.*

By L. H. Tiffany. Harper & Brothers, New York and London. $1.50 (unbound; punched for looseleaf notebook). vi + 240 pp. 1946.

In the exercises of this excellent manual—designed for the presentation, in a simple, usable, and thought-provoking manner, of the materials for a well-rounded year course in college botany—the problem approach is emphasized, and the student is encouraged by every device known in teaching techniques to make independent observation and interpretation of the structures, processes, and environmental relations of plants.

Diagrams and drawings accompanying each topic are not mere outlines or partially completed sketches, but detailed drawings very carefully and accurately prepared. The entire manual is as carefully illustrated as a text-book, some illustrations and drawings being intended primarily for interpretation and discussion, others for labeling.

The manual is presented in loose-leaf form so as to afford, as the author explains, the greatest latitude for additional exercises, for variety of sequences of topics, and opportunity for individual expression in the presentation of reports.

Some of the major topics dealt with, each accompanied by a very complete list of questions and problems, include: (1) external features of leaves and buds as an aid in the classification of trees and shrubs—with accompanying keys to common species of trees, one based upon leaf characters, the other on bud characters; (2) plants of lawns and pastures; (3) autumnal aspects of plants; (4) the structure and physiology of cells; (5) the making and use of organic foods in plants; (6) the external and internal structure of stems and roots; (7) interrelationships between the parts of plants; (8) reproduction in flowering plants; (9) plant heredity; (10) the great groups of plants; (11) some features of plant geography and paleobotany; (12) evolution. A general review, with a complete list of discussion questions, and four appendices conclude the manual.

Suggested improvements that might contribute somewhat to the popularity of the manual, are (1) a reduction in the number of questions and problems accompanying each topic, for there is a tendency here to repetition; (2) greater opportunity afforded for the delineation of structural features, either by the completion of drawings, or by suggested drawings, diagrams, or reconstructions to be prepared by the student.

LaDema M. Langdon

Pure Cultures of Algae: *Their Preparation and Maintenance.*

By E. G. Pringsheim. University Press, Cambridge; The Macmillan Company, New York. $1.75. xii + 119 pp. 1946.

The purpose of this little book is to give a detailed account of the author's methods of obtaining pure cultures of algae and the proper maintenance of such cultures.

After the frontispiece, a portrait of M. W. Beijerinck, who is considered by the author to have laid the foundations of general microbiology along with Pasteur and Winogradsky, there is a foreword by the distinguished British algologist, F. E. Fritsch. Here Fritsch points out the significance of E. G. Pringsheim's contributions to the field of algae culture, particularly his ingenuity in fitting his culture technique to the needs of each particular organism.

After a short preface outlining the aid which pure and unialgal cultures can bring to an elucidation of fundamental problems of ecology, hydrobiology, fisheries, genetics, etc., there is an introduction that deals mainly with the history of the field. There follows a chapter on the selection of algae to be cultured and the use of preparatory cultures, special enrichment cultures, and soil-and-water cultures. The development of the last-named type of culture is due primarily to Pringsheim and is considered by many to be his most important contribution to the field of General Microbiology.

Chapter three deals with the implements and media used in growing algae. In this section there are discussions of such topics as water and the containing vessels, mineral solutions, soil and peat extracts, organic media, and the use of gelatine, agar, and silica gel as solidifying agents. The following two chapters describe in detail the plating and pipetting or washing methods for the obtaining of pure, unialgal cultures. Following a very short resumé of the methods of preparing pure cultures, there is a section dealing with the treatment and utilization of cultures. Here are discussed the proper environmental conditions under which the cultures should be maintained and the diverse uses to which such cultures may be put.

The final chapter discusses the methods best adopted for obtaining cultures of representatives of the various taxonomic groups of the algae. There is a bibliography and short index.

The book is well written for an author whose native tongue is not English. It is well documented throughout, and presents in careful, almost elementary style, the steps to be followed in the various procedures outlined. It should prove useful to both the general microbiologist and algologist.

F. K. Sparrow

Pore Fungi.

By William Alphonso Murrill. Published by the author, Gainesville, Florida. $3.00 (paper). 110 pp. 1946.

A paper-covered "illustrated guide" composed of approximately one-third punkies and two-thirds polypores and other fungi. Hardly a bargain at $3.00, even in these days of inflation.

F. K. Sparrow

Hepaticae of North America. *Part IV. University of Washington Publications in Biology, Volume 6, Number 4.*

By T. C. Frye and Lois Clark. University of Washington Press, Seattle. $2.50 (paper). iv + pp. 565–733. 1946.

Part IV of this work comprises the treatment of six families of the North American liverworts: Scapanioideae, Lepidozioideae, Calypogeoideae, Raduloideae, Pleurozioideae, and Porelloideae. Three new combinations are made, and a single new variety is described. The new combinations are: *Scapania bolanderi* var. *americana* (K. Muell.), *Calypogeia arguta* var. *sullivantii* (Aust.), and *Porella platyphylla* var. *platyphylloidea* (Schw.). The new variety is *Scapania subalpina* var. *haynesiae.*

Hugh M. Raup

The Genus Bazzania in Central and South America. *Annales Cryptogamici et Phytopathologici (incorporating Annales Bryologici), Volume 3.*

By Margaret Fulford. The Chronica Botanica Company, Waltham, Massachusetts; G. E. Stechert and Company, New York. $5.00 (paper). xvi + 175 pp. 1946.

Margaret Fulford's masterly monograph of the Central and South American hepatic genus *Bazzania* is a com-

panion piece to her earlier monograph of the genus in Canada and the United States, published in 1936. In the course of the work she examined material from the principal cryptogamic herbaria of the world, including a great many type specimens. Forty-six species are recognized in the present work, and 21 are listed without description. Types or authentic material of the latter were not available due to the war. No new species or varieties are described in the monograph, but there are 17 new nomenclatorial combinations, as follows: *B. Herminieri* (Steph.), *roraimensis* (Steph.), *pallide-virens* (Steph.), *chilensis* (Steph.), *taleana* (Steph.), *Glaziovii* (Gottsche), *tricuspidata* (Steph.), *latidens* (Gottsche), *longa* var. *papillata* (Steph.), *Wrightii* (Gottsche), *Fendleri* (Steph.), *armatostipula* (Steph.), *Skottsbergii* (Steph.), *asperistipula* (Steph.), *canelensis* (Steph.), *Tayloriana* (Mitten), and *Stephani* (Jack). Copious descriptions of the various species are given, with discussion of their habits, distribution, nomenclature, and ecology. Each is illustrated by detailed line drawings. The paper concludes with a list of literature and an index to names.

All American species of *Bazzania* are placed in one or the other of two subgenera which are distinguished from one another by the number of teeth on the leaves: Bidentatae and Tridentatae. The Tridentatae are further subdivided into 5 sections: Grandistipulae, Connatae, Fissistipulae, Appendiculatae, and Vittatae. The geographic distribution of these groups, and of the individual species which compose them is not well known. Fulford restricts her discussion of distribution to less than two pages, saying that present knowledge consists of a geography of collectors rather than of species.

HUGH M. RAUP

TREES IN BRITAIN: *Wild, Ornamental and Economic and Some Relatives in Other Lands.*

By L. J. F. Brimble. Macmillan and Company, London; The Macmillan Company, New York. \$4.50. x + 352 pp. + 8 plates. 1946.

Trees in Britain is a companion volume to the author's *Flowers in Britain* which was published in 1945. It is done in much the same manner, and printed in a similar format, and with equally profuse illustration. The book is a popular, readable guide to trees commonly seen in the British Isles. Both native and introduced species are treated. Part I is an Introduction containing a general review of the plant kingdom, some notes on the kinds of seed plants, discussions of the structural characteristics of broad-leaved and coniferous trees, and an introduction to the classification of plants. The main body of the book is in two parts: one on conifers and other gymnosperms, and the other on broad-leaved trees (angiosperms). Treatments of genera and species are not in abbreviated "manual form" but in a pleasingly simple and direct prose style. In spite of this, it is easy to find things in the book because of adequate subheadings and the use of different type faces. Common names are in boldfaced type, and Latin names in italics. Furthermore, the arrangement of families and genera follows, in general, one of the standard systems of classification. For the angiosperms, as in *Flowers in Britain*, Brimble follows Hutchinson.

Common recognition characters are given for most of the species, with notes on their flowering and fruiting habits, and the uses to which they are put. The book is replete with the folklore of British trees—their significance in history, and accounts of very old trees that have figured in stories and historic events. There are many well-chosen quotations from literature, both prose and verse. Illustrations consist of line drawings, half-tone reproductions of photographs, colored plates of landscape paintings that figure trees prominently, and colored plates of detailed drawings to help in identifying species. There are also many reproductions of drawings of famous British trees, done by Lonsdale Ragg. The line drawings were made by Mr. Brimble himself. The half-tones are not well printed in many cases, but criticism seems hardly fair, in these days of paper shortages, for the fault probably lies in the quality of the paper rather than in the printing.

Brimble's books have just claim to popularity, and could profitably be emulated in this country.

HUGH M. RAUP

A MANUAL OF SOUTHWESTERN DESERT TREES AND SHRUBS. *University of Arizona Bulletin, Volume XV, Number 2. Biological Science Bulletin Number 6.*

By Lyman Benson and Robert A. Darrow. University of Arizona, Tucson. \$3.00 (paper); \$2.00 each for orders of ten copies or more. 411 pp. 1945.

This sumptuously printed manual is the second in a series on the flora of Arizona and the Southwest published by the University of Arizona. It is semi-popular in nature, covering all trees and shrubs native to the deserts of California, Nevada, Utah, Arizona, New Mexico, and Texas. There are 411 pages of printed matter and 116 plates. Of the latter, 46 consist of line drawings to illustrate various species, 25 are black and white half-tones, 35 are range maps, and 9 contain color photographs. The distribution maps cover 102 of the species. All of the plates are clear and well-executed.

The Introduction to the book contains, in addition to the usual directions for the use of the keys and catalogue, a brief but informative sketch of the general plant geography of the southwestern deserts. There are discussions of climate and physiography, floristic

regions, and of vegetation types adjacent to the deserts. In the list itself both Latin and common names are given for each species, followed by a brief statement of recognition characters. A more detailed description is given in smaller type, with notes on habitat, geographic distribution, and economic aspects. Synonyms are not given in the main text, but are arranged alphabetically in an appendix. All plant names are indexed at the end of the book.

The taxonomic evaluation of a book of this kind must be left to special students of the region covered, but as a useful tool for anyone whose knowledge of the desert flora is limited, this volume should prove invaluable. Its excellent and abundant illustrations, the brevity and clarity of its descriptive matter, and its wealth of useful lore about the plants should make it popular among students, collectors, and casual travellers.

HUGH M. RAUP

AN ILLUSTRATED MANUAL OF PACIFIC COAST TREES. *With lists of trees recommended for various uses on the Pacific Coast.*

By Howard E. McMinn and Evelyn Maino; lists of trees by H. W. Shepherd. University of California Press, Berkeley. $4.00. xii + 409 pp. 1946.

The trees of the Pacific coast, from southern California to British Columbia, are covered by this excellent little manual. It is of suitable size to be used as a field book, and is bound in a waterproof cover. The end papers carry maps—those in the front for California, and those in the back for Oregon, Washington, and southern British Columbia. The book is designed not only for casual travelers, foresters, teachers, landscape architects, and guides, but also for professional botanists who need to identify Pacific Slope material.

The Introduction consists first in a general discussion of the gross morphology and classification of plants, of use chiefly to beginners. Second, there is a brief account of the geographic distribution of Pacific coast trees, with some notes on their probable origins. The Merriam life zone system is the basis for the geographic arrangement. A very useful section is devoted to an outline of the geographic origins of the many introduced trees that are treated in the book.

Diagnostic keys are given within the genera, and a comprehensive key to the genera appears at the beginning of the list. Most of the species are illustrated by simple line drawings of such parts as are of particular use in identification. Palms and palm-like trees are illustrated by photographs. Common names are taken mainly from *Standardized Plant Names*, and only enough synonymy is included to make the book referrable to other western manuals. Families are arranged according to Engler and Prantl in *Die natürlichen Pflanzenfamilien*, but within the families the genera are arranged alphabetically. At the close of the book are a glossary of botanical terms and a list of "additional native species which occasionally are tree-like." Finally there are lists of trees recommended for various uses on the Pacific coast. These lists were prepared by H. W. Shepherd, Associate Professor of Landscape Design at the University of California, and should add greatly to the general usefulness of the book. An index covers all plant names used in the text.

HUGH M. RAUP

FORMULAIRE TECHNIQUE DU BOTANISTE PRÉPARATEUR ET VOYAGEUR. *Ce qu'il faut Savoir pour récolter, préparer, expédier, conserver et présenter les plantes et objets d'origine végétale. Savoir en Histoire Naturelle, Volume X. Guides Techniques du Naturaliste, Volume III.*

By A. Guillaumin. Paul Lechevalier, Paris. 52 fr. (paper). 139 pp. + 2 plates. 1942.

This manual is designed to give the layman pertinent information regarding the establishment of botanical collections and exhibitions. Living plants, seeds, herbarium material, woods, medicinal and perfume plants, anatomical and histological material, and ethnographic objects of vegetable origin are discussed separately.

Part I deals with methods of collecting, pressing, drying and shipping; Part II is concerned with the protection of herbarium specimens and other museum material, including books; Part III discusses briefly the functions of museums, botanical exhibitions, herbaria, and botanical gardens. A short account is given of the more important herbaria and botanical gardens of the world, both past and present, with special reference to the collections at the Paris Museum.

ALBERT F. HILL

PLANT PHYSIOLOGY

LA CULTURE DES TISSUS: *Une Voie Nouvelle en Biologie Végétale. L'Avenir de la Science, Number 21.*

By R.-J. Gautheret. Librarie Gallimard, Paris. 190 fr. (paper). 203 pp. + 32 plates. 1945.

As No. 21 in Jean Rostand's collection "The future of science," this little volume is intended for the intelligent lay public as well as for scientists. It is interestingly written and beautifully illustrated, and although it suffers somewhat from the difficulties inherent in the poor paper available today, it is well worth anyone's perusal. When one realizes that war overwhelmed France early in 1940, hardly more than a year after the publication of the first three papers describing successful cultures of plant tissues (White, December 1938;

Gautheret, January 1939; Nobécourt, February 1939) and that therefore most of the investigations upon which this book is based were carried out under the difficult conditions of occupied Paris, it is with a feeling of great respect that one notes the extent and quality and balance which Gautheret has been able to give to the European development of this most interesting and important subject; for it is, as the book's subtitle implies, truly a new approach in plant biology, an approach which has already had considerable influence upon our thinking in morphogenesis, in tissue nutrition, in pathology, and elsewhere.

The introductory chapter is historical and interesting to the general reader. The following chapters on techniques, on the morphological characteristics of cultures, and on physiological studies are somewhat more technical; whereas the last chapter, on possible future trends, is again of general interest.

Haberlandt, forty-five years ago, predicted that the cultivation of plant tissues would "cast many interesting sidelights on the peculiarities and capacities which the cell, as an elementary organism, possesses, . . . [and would] make possible conclusions as to the interrelations and reciprocal influences to which the cell is subjected within the multicellular organism." Gautheret has contributed largely to the development of methods for the realization of this prediction, and in this book he has presented some of the progress so far made. He is to be congratulated on a task well done.

PHILIP R. WHITE

ECONOMIC BOTANY

GENERAL HORTICULTURE: *Principles and Practices of Orchard, Small Fruit, and Garden Culture.*

By Thomas J. Talbert. Lea & Febiger, Philadelphia. $4.00. 452 pp. 1946.

In the preparation of this work—a rewriting and expansion of *Fruit Crops*, published in 1939—the major objective was the presentation of a clear, concise, modern treatise on general horticulture for the benefit of both students and producers. In addition to the topics usually discussed special chapters dealing with basic problems have been included. The applied phases of the science are especially emphasized, since this text is intended to be a practical and scientific guide to the business of horticulture. The language used, though technically accurate, is simple and understandable. Illustrations are freely used to supplement the discussion, and lists of selected references are appended to each chapter.

The scope of the work may best be judged by listing the contents: The Horticultural Industry; Factors Affecting Fruitfulness; Varieties, Pollination and Fruit Thinning; Propagation; Soils, Locations and Plantings; Soil Management and Fertilization; Pruning Deciduous Fruit Trees; Insects of Fruit Crops; Diseases of Horticultural Crops; Spraying and Dusting; The Pome Fruits; The Stone Fruits; Grape Culture; Strawberry Culture; Cane and Bush Fruit Culture; Nut Tree Culture; Growing Vegetables; Beautifying the Home Grounds; Tropical and Subtropical Fruits; and Distributing Horticultural Crops.

ALBERT F. HILL

GROUNDS FOR LIVING. *The Home Dweller's Compleat Guide to His Lawns, Trees, & Gardens.*

Edited by Richard B. Farnham and Van Wie Ingham; introduction by Haydn S. Pearson. Rutgers University Press, New Brunswick. $2.50. x + 334 pp. 1946.

This readable book will appeal to the ordinary citizen who wants to make the most of his home surroundings. Without the use of too technical words or details, and relying rather on numerous charts, diagrams and illustrations, it presents a well rounded picture of small-scale horticultural practice in its various aspects, and points the way to the happiness to be gained by outdoor living.

The nine chapters, all contributed by specialists in their respective fields, deal with the following subjects: the home setting with instructions for landscaping; the lawn and its care; shade trees; annuals and perennials; specialities such as roses, chrysanthemums, and gladioli; the essentials of successful vegetable gardening; fruit trees; soil and fertilizers; and outdoor construction.

ALBERT F. HILL

BEGONIAS AND HOW TO GROW THEM. *Issued under the Auspices of the Massachusetts Horticultural Society. By Bessie Raymond Buxton. Oxford University Press, New York.* $2.25. xii + 163 pp. + 31 plates. 1946.

Begonias have had their enthusiastic friends for many years, and more recently a society and a magazine to further their interests. Now comes a book, written by a specialist in the field, under the auspices of the Massachusetts Horticultural Society, which presents to the layman a wealth of information regarding these attractive plants.

The 200-odd species and varieties are described in detail with many illustrations and text figures and much historical material. Other chapters deal with soils and fertilizers, seed-sowing methods, propagation from cuttings, pests and diseases, tuberous-rooted begonias,

and begonia shows. A brief account of the American Begonia Society is appended.

ALBERT F. HILL

NEW ICONOGRAPHY OF THE CAMELLIAS: *Containing the Figures and the Descriptions of the Rarest, the Newest and the Most Beautiful Varieties of This Species. 1848–1860.*

By Alexandre Verschaffelt, translated from the French by E. A. McIlhenny. Published by E. A. McIlhenny, Avery Island, Louisiana. $3.50. ix + 318 pp. 1945.

This translation makes available to Camellia lovers and the general public the descriptive material contained in the thirteen original volumes of Verschaffelt's classic work, long unobtainable. 623 varieties are described, many of which are to be found in the trade today under different names. With the original descriptions now available, it should be possible to clear up much of the existing confusion in Camellia names.

ALBERT F. HILL

FRUITS OF HAWAII: *Description, Nutritive Value, and Use. University of Hawaii Agricultural Experiment Station Bulletin 96.*

By Carey D. Miller and Katherine Bazore. University of Hawaii, Honolulu. $1.00 (paper). 129 pp. 1945.

This little booklet is a revised and enlarged edition of the earlier Bulletin 77 published in 1936. It deals primarily with the utilization of 29 of the most readily available of Hawaiian fruits. Brief notes concerning their description, history, nutritive value, availability in Hawaiian markets, and use are followed by numerous tested recipes. An appendix presents general directions for canning and jelly making, together with data regarding the vitamin and mineral contents of the fruits.

BEHOLD OUR GREEN MANSIONS. *A Book about American Forests.*

By Richard H. D. Boerker. The University of North Carolina Press, Chapel Hill. $4.00. xv + 313 pp.; 96 plates. 1945.

Sound use of natural resources in a government of the people can be achieved only through enlightened public opinion based on fact rather than on fancy. *Behold Our Green Mansions* presents and interprets, for all who will read, the facts requisite to an understanding of one of America's greatest and most glorious resources—her forests.

This is not just another book on forest conservation. It is a remarkably accurate and unbiased account of our forests, past and present. The author has avoided the extreme view that conservation necessitates withdrawal of forests from all use, as well as the juvenile notion that forestry is "planting a little tree for each big one cut down."

Those who think of forests in terms of lumber alone may be surprised to learn of the many other services rendered. Recreational opportunities in wide variety are afforded, and every forest serves as a home for wildlife. Forests are particularly efficient in preventing soil erosion and regulating stream flow. In many parts of the West the forests supply important amounts of forage for domestic livestock.

Everyone who wishes to learn what forests and forestry mean to them will find the answers in *Behold Our Green Mansions.* The large number of carefully selected and well-reproduced illustrations add greatly to the appearance and utility of the book. An adequate index makes reference to specific subjects easy.

H. J. LUTZ

THE FRIENDLY EVERGREENS.

By L. L. Kumlien. D. Hill Nursery Company, Dundee, Illinois. $6.00. 237 pp. + 1 plate. 1946.

This attractive and profusely illustrated volume is the work of a practical nurseryman rather than a horticultural authority. Drawing on many sources of information, the author has retold the story of evergreens in simple, non-technical language designed to appeal to the general public.

Although some 180 varieties are described and illustrated, many in color, the book is far more than a nursery catalogue. The greater part is filled with interesting information on all phases of evergreens and their utilization. Their classification (based on the second edition of *Standardized Plant Names*), morphological characteristics, methods of seed collecting, propagation and culture, diseases and injuries, and uses in landscape design are only a few of the topics discussed.

ALBERT F. HILL

LONGLEAF PINE: *Its Use, Ecology, Regeneration, Protection, Growth, and Management.*

By W. G. Wahlenberg. Charles Lathrop Pack Forestry Foundation, Washington, D. C., in cooperation with the Forest Service, U. S. Department of Agriculture. $5.00. xxii + 429 pp. + 49 plates. 1946.

This excellent monographic treatment of one of the most important trees of the United States is an outstanding contribution to forest literature and may well serve as a model for future studies of other economic species. The amount of material gathered together between the covers of this volume is amazing. The treatment is highly comprehensive, and the data are adequately digested, interpreted, and presented.

All phases of the life history and ecological relationships of *Pinus palustris* Mill. are discussed, together with problems of management and utilization. Among the topics considered are the anatomical characteristics, silvical peculiarities, resources, uses and properties, natural distribution, the critical role of fire in regeneration, seeds, seed beds and seedlings, problems of natural reproduction, artificial regeneration, protection from fire and from insects, diseases, animals and climatic injuries, naval stores operations, growth and yield of trees and stands, and the management of the forests.

Appendices are included which give further data on the common names, the characteristic flora of the longleaf pine belt, special uses of the land, density rules, strength of the wood, together with stand, volume, diameter, and height tables. An adequate glossary and a bibliography of 637 titles complete the work.

This book should serve as the standard reference work on the longleaf pine and should be an indispensable working tool for any one interested in forest management in the southeastern states, especially those concerned with the rehabilitation of the longleaf pine lands.

ALBERT F. HILL

INVESTIGATIONS OF GUAYULE (PARTHENIUM ARGENTATUM GRAY) IN SOUTH AUSTRALIA. *Bulletin Number 192.*

By R. L. Crocker and H. C. Trumble. Council for Scientific and Industrial Research, East Melbourne, Australia. Free upon request (paper). 44 pp. + 12 plates. 1945.

These investigations under the joint supervision of the Council and the Waite Agricultural Research Institute were initiated in 1942 at Adelaide, to assess the possibilities of producing guayule on a large scale in South Australia. Centers at which climatic conditions and test plantings were studied were confined to the vicinity of Adelaide and to the north and west of that city. The project became essentially investigational because difficulties encountered in seed germination and establishment in the nursery and in field establishment and maintenance made imperative a full investigation of the factors concerned. The report in this bulletin is limited to these problems. Progress reports received from the U. S. Dept. Agric. Emergency Rubber Project, Salinas, Calif., aided in their solution. The first seeds used came from the Plant Introduction Garden of the Division of Plant Industry, C.S.I.R., Canberra. Later, seeds were received from the U.S.D.A. Since direct seeding was unsuccessful, the conventional and expensive method of seed germination, seeding and growth in a nursery, and subsequent transplantation in the field was followed. Maximum germination with U. S. seeds was obtained by the following technique: (1) mechanical agitation in a 5 per cent solution of chloride of lime, (2) centrifuging to 3.7 times original dry weight, (3) presprouting in light at 20°C. October and November were the best months for seeding. For maximum establishment in the field following transplantation, adequate topping was the most important single factor. Seedlings were cut back completely to the stem collar. For growth and development in the field, the temperature should be above 15°C. and there should be a supply of moisture in the surface soil throughout the spring months. Only limited areas in South Australia (excepting irrigated land) have the necessary rainfall. Soils must be of light texture and good fertility. Since use of sprays was too expensive, weed control was effected by well-timed regular cultivations plus some hoeing. The growth rate of guayule was lower than that of common native fodder shrubs of arid regions. Comparison was made with saltbush (*Atriplex vesicarium*) and bluebush (*Kochia georgii*). The economic possibilities of guayule rubber production under South Australian conditions depend partly upon determinations of yield when the shrub matures, determinations not yet available at the time this report was made.

A. D. BERGNER

GENERAL AND SYSTEMATIC ZOOLOGY

ANIMAL BIOLOGY. *Third Edition.*

By Robert H. Wolcott. McGraw-Hill Book Company, New York and London. $4.00. xviii + 719 pp. 1946.

In many ways this is an admirable book. The text is generally straightforward, interesting, and up to date. A paramecium will conjugate only with an individual of another mating type; insects are controlled by DDT; etc. Undoubtedly a student would obtain a fairly detailed knowledge of one or more "type" organisms in each of the major phyla, besides a general view of the characteristics and diversity to be found within each phylum. In addition, there are special chapters, although sometimes only three or four pages long, on matter, energy, cells, ecology, paleozoology, embryogeny, life, classification, and other topics. An unusual and commendable feature is an annotated list of available films to accompany each chapter.

As often happens in volumes of this size, it has its weak spots. Spiremes still infest cells about to divide. A student who learns about meiosis from this text will have several things to unlearn later. Some of the statements about earthworms are only partly true. The term tropism is defined in the glossary in the usual way, is used in the text first (p. 83) in this usual sense, but then later (p. 551) in a very different and certainly unetymological sense. There are a distressing number of vague, sweeping, and not too accurate generalities. "All animal activities seem to be rhythmic." "Individuality is universal among animals." The chordates are the "highest" phylum because the most "efficient." There are some surprising omissions. Despite considerable space given to animal behavior, reflexes, habits, intelligence, and kindred topics, there is no specific mention either of Pavlov or of conditioned reflexes. The amnion is not given as one of the adaptations fitting reptiles for the conquest of the land, although scales are. But all these are essentially details.

The prime assumption on which this book is constructed is that taxonomy—zoological taxonomy, that is—furnishes the best framework on which to organize the modern science of living things. There are those of us who cling to this idea; but the present reviewer must confess that it seems to him an obsolescent, if not altogether obsolete, approach. How can it be otherwise when taxonomy no longer occupies the central place in biological or even zoological thought that it held throughout much of the nineteenth century? The steady advances in cytology, in genetics, in evolutionary theory, in our knowledge of respiration, of vitamins, of protein metabolism, of enzyme action, and in a dozen other fields all push the center of biological interest and of actual importance farther and farther from taxonomy. Simultaneously, modern discoveries are rendering the distinction between animals and plants of less and less basic scientific significance. The primary importance of *Neurospora*, to choose but a single example, is most certainly not that it belongs among the ascomycetes. The truth would seem to be that taxonomy will always constitute an important part of biology, but not the framework on which the entire science is to be hung.

As a result of the attempt to maintain taxonomy in a central position, Wolcott's text inevitably falls between two stools. It seems a pity to have to say this about a book that is evidently the product of such considerable labor. Nevertheless, as a presentation of either the invertebrates or the vertebrates, this book is not comparable to any of the standard texts in those fields. On the other hand, as a presentation of biological principles the book is demonstrably inferior to any of a dozen volumes that treat of biology unencumbered by taxonomic limitations. Out of over 700 pages, natural selection and mutation receive one paragraph each, the vertebrate excretory systems and the endocrine glands two pages each, while vitamins are covered in a page and a half. The material on animal behavior, on reproduction and development, and even on classification is fuller, though still truncated, widely scattered, and sometimes unnecessarily repetitious, contradictory, or out of order. Conjugation and endomixis in *Paramecium* are discussed, with elaborate diagrams of nuclear behavior, some time before mitosis or meiosis are presented. The carbon and nitrogen cycles are scarcely more than diagrams. Perhaps it would be fair to say that there are really two books here, each one crowding and distorting the other.

GAIRDNER MOMENT

ANIMAL CAMOUFLAGE. *Pelican Books.*

By E. M. Stephenson in collaboration with Charles Stewart. Penguin Books, Harmondsworth, Middlesex; and New York. 1 s. (paper). 160 pp.; 8 plates. 1946.

The authors have provided an excellent account in non-technical language of a much broader biological field than their title might at first indicate. Not only do they describe examples of coloration for concealment and of mimicry in a great variety of environments, but they have also considered the entire scope of the problem of the relations between light, color, and vision. The problem of color change in hermit crabs, prawns, cuttlefish, chameleons, frogs, and fishes occupies a big place in the discussion, both direct and indirect responses, and control both by way of the nervous system and by means of hormones being set forth in clear relations. The roles of protective and warning colors in the struggle for existence are also discussed as a step to understanding the real significance of animal camouflage.

Stewart, in an Epilogue, takes the responsibility for the philosophical implications in the work, and says that "the authors have not been consciously either teleological or mechanistic. . . .Therefore when we say, 'a spider mimics an ant,' 'crawling in a deliberate fashion,' 'imitation is employed,' the terms just convey the appearance of the matter. This book is meant for common-sense people, and not for those whose complexes compel them to talk mostly in a special jargon." Those who have tried to write for "common-sense people" may agree, yet it need not lead us to approve, as the authors seem to do, the more mystic flourishes of Ouspensky's thought, or to conclude that since we know that "Nature achieves these effects of decoration and camouflage partly by minute changes, but also by sudden and often strange mutations" that therefore "these facts incline us to presume the existence of some power in Nature herself which directs the appearance and stabilising of new traits," probably "a form of sentience, or respon-

siveness, [that] must be allowed to all matter." Is this more than a new twist to the inheritance of acquired characteristics? Or is it Bergson's élan vital? It seems too bad that so excellent an achievement should be marred by the intrusion of such spectres!

BENTLEY GLASS

INSECTS OF THE PACIFIC WORLD. *The Pacific World Series.*

By C. H. Curran. The Macmillan Company, New York. $3.75. xv + 317 pp.; 8 plates. 1945.

This little volume is one of the "Pacific World Series" prepared for the armed services. To give a thorough account of the immense number of insects occurring in the Pacific area in a volume of this size is an impossible task. The author, with the help of several specialists, has restricted himself to a general popular treatment of the larger orders of insects and their relatives, emphasizing the biologies of those which are most likely to be noticed because of their bizarre forms or because of their transmission of human diseases.

It is unlikely that anyone using this book will be able to identify any particular species, even with the aid of the figures, but such was not the intent of the author. In general, the discussions of the orders and the more important families are written in simple language, yet some of them contain technical terms which are not explained anywhere in the text.

Since this volume was intended, apparently, for the use of persons having no knowledge of entomology, it is surprising that less than six pages are devoted to a general characterization of insects and their relatives in the first chapter. The following eleven chapters deal with the various orders: Diptera; Hymenoptera, by H. F. Schwarz; Lepidoptera; Coleoptera, and Hemiptera, by J. C. Pallister; Homoptera; Odonata, by Mrs. E. B. Klots; "Neuropteroids"; Orthoptera; "The Small Orders"; The Arachnids and Allies, by W. J. Gertsch. Chapter 13, on Insects and Disease, is very brief and contains less information on the subject than the average member of the armed services received in his training program. The final chapter, dealing with the collecting, preserving, and shipping of insects, is extremely brief and has little information for any member of the armed services who happened to have no access to the materials suggested and would have to rely more on his ingenuity and initiative.

It is regrettable that more illustrations of insects were not included in this volume, especially of the forms generally distributed in the Pacific area. Outside of the Lepidoptera and Hymenoptera, very few specific names of insects are mentioned.

ROBERT MATHESON

CHECK LIST OF THE CICADELLAE (HOMOPTERA) OF AMERICA, NORTH OF MEXICO. *Graduate School Studies: Biological Science Series, Number 1.*

By Dwight M. DeLong and Dorothy J. Knull. The Ohio State University Press, Columbus. $1.50 (paper). vi + 102 pp. 1945.

The present list is of particular value to specialists in this most important family and, also, to general workers in the field of economic entomology. It is a revision of the 1937 list prepared by DeLong and Caldwell and includes corrections of errors and omissions in the first list, new synonymy, and additional genera and species described to May, 1945. A number of new combinations or arrangements not previously published are given. In all, the present list contains 175 genera and 2,276 species, varieties, and subspecies occurring north of Mexico.

A brief introduction explains the scope and mechanics of the list. This is followed by a systematic arrangement of subfamilies and genera. In the main body of the work, which follows in the same systematic arrangement, the species are listed alphabetically under each genus, subgenus, or group. The subspecies, varieties, and recent synonyms are listed under the species with which they are now associated. The genotypes are given in all cases. In the case of species now placed in a different genus, the original genus under which a species was first described is in parentheses after the citation. Since the bibliographical citations are abbreviated by using a key number to publications, a key list of publications is appended. A useful feature of this work is the list of suggested generic papers on North American Cicadellidae. An index to genera is also included.

ROBERT MATHESON

THE NORTH AMERICAN CLEAR-WING MOTHS OF THE FAMILY AEGERIIDAE. *Smithsonian Institution, United States National Museum Bulletin 190.*

By George P. Engelhardt. United States Government Printing Office, Washington, D. C. 75 cents (paper). vi + 222 pp. + 32 plates. 1946.

Forty-five years have elapsed between the appearance of Beutemüller's *Monograph of the Sesiidae of America North of Mexico* (*Mem. Amer. Mus. Nat. Hist.*, 1:217-352; pls. xxix-xxxvi. 1901) and the present work. It is unfortunate that in the present work no reference is made to the first revision as a unit; the two papers seem well adapted to be used together, the figures of the adults of the present paper supplementing those of the first revision by Beutemüller.

The present revision of the family Aegeriidae places the taxonomy of the group on a firm basis, comparable in nature with the other revisions of various "micro"

families published by the workers of the United States National Museum. To the working entomologist the genera seem too finely drawn; it might have been better if what the author calls "Groups" had been given generic rank, and the genera described under the various "Groups" had been given subgeneric rank. However, this is only a suggestion. A most valuable part of the work is the bringing together of all the known data on the life histories and food plants of the North American species.

ROBERT MATHESON

CHECKLIST OF THE COLEOPTEROUS INSECTS OF MEXICO, CENTRAL AMERICA, THE WEST INDIES, AND SOUTH AMERICA. *Part 4. Smithsonian Institution, United States National Museum Bulletin 185.*

Compiled by Richard E. Blackwelder. United States Government Printing Office, Washington, D. C. 50 cents (paper). iv + pp. 551–763. 1946.

Part IV of this checklist treats of the families Cerambycidae, Chrysomelidae, and Bruchidae.

MONOGRAPH OF THE FAMILY MORDELLIDAE (COLEOPTERA) OF NORTH AMERICA, NORTH OF MEXICO. *Miscellaneous Publications, Museum of Zoology, University of Michigan, Number 62.*

By Emil Liljeblad. University of Michigan Press, Ann Arbor. $2.00 (paper). 229 pp. + 7 plates. 1945.

It is indeed unfortunate that this monograph, the first treatise on the family in North America since LeConte's *Synopsis* of 1862, has had to wait sixteen years for publication. In the intervening years it has been practically impossible to identify correctly the members of this interesting family of beetles. With the appearance of this work there should be renewed interest in the study of this family.

Liljeblad includes 193 species, distributed among 15 genera, in this work. Thirty-nine species and two genera are described as new and four genera are added to the North American fauna. For almost every species there is a thorough description of the external morphology, followed by remarks on variation, taxonomic relationships, and distribution records. Over 100 species are illustrated, many of them by drawings of the whole beetle, as well as details of legs, antennae, and palpi. The keys depend largely on color characters, especially in the genus *Mordellistena*, and become rather unwieldy at times.

In a work of this size one would expect some information on the biology of the group, but the author restricts himself in the introduction to a very brief discussion of the taxonomic characters. No new characters were found in the course of this study. Male genitalic characters appear to offer good differentiation in the *Anaspinae*, according to the figures. One wonders if they have been given proper consideration in the study of the rest of the family.

ROBERT MATHESON

REVIEW OF THE NEW WORLD SPECIES OF HIPPODAMIA DEJEAN (COLEOPTERA: COCCINELLIDAE). *Thomas Lincoln Casey Fund. Smithsonian Miscellaneous Collections, Volume 106, Number 11. Publication 3855.*

By Edward A. Chapin. The Smithsonian Institution, Washington, D. C. 35 cents (paper). 39 pp. + 22 plates. 1946.

Many of the genera of lady-bird beetles exhibit striking variation in color patterns. This has made them favorite subjects for describers of subspecies, varieties, and aberrations in the past. In recent years more attention has been paid to the evolutionary significance of these variations. Chapin has correlated male genitalic characters with the color patterns in his study of the genus *Hippodamia*. He divides the genus into 6 groups with a total of 17 species, represented by 32 subspecies and 2 varieties. Three new subspecies are described. This work is especially valuable because of the illustrations, which included 180 figures of color pattern variations, 46 figures of male genitalia, and 20 distributional maps. Despite the large number of specimens examined (over 11,000), this study is stated to be of a preliminary nature, and no keys are included. It is unfortunate that the majority of the names formerly proposed for forms in this genus are not included in the synonymies.

ROBERT MATHESON

THE MOSQUITOES OF THE SOUTHERN UNITED STATES EAST OF OKLAHOMA AND TEXAS. *The American Midland Naturalist Monograph Number 3.*

By Stanley J. Carpenter, Woodrow W. Middlekauff, and Roy W. Chamberlain. The American Midland Naturalist, University of Notre Dame, Notre Dame, Indiana. $4.00. viii + 292 pp. 1946.

In the Foreword the authors state that they have attempted to give an up-to-date account of the mosquitoes occurring in the southern United States east of Oklahoma and Texas. This they have done most satisfactorily. They give brief accounts of the bionomics of mosquitoes and their relation to disease, a rather full account of the collecting, preserving, and mounting

of mosquitoes in all stages, and a fairly detailed description of the various morphological structures used in classification. In their illustrations and descriptions of the male they use that unfortunate term, male *terminalia*. To the reviewer this term is anathema—all our standard dictionaries define Terminalia as the festival of the god Terminus celebrated by the Romans on Feb. 23rd of each year. Why not adhere to the generally used term, male genitalia, which can include all those structures associated with the male reproductive organs or only those which are external?

In the systematic part of the monograph excellent keys are given to females, males (based on genitalic characters), and to larvae (fourth stage). Practically every species is illustrated, and the descriptions are adequate for identification. The illustrations are beautifully done. Under each species there is a brief statement of its bionomics and the details of its known distribution. These are valuable contributions as they are based on the extensive work done during the war period by various members of the Sanitary Corps. A bibliography of 188 titles and an index complete the volume. The publishers are to be congratulated on the excellent make-up and the quality of the paper and binding.

ROBERT MATHESON

ÉTUDES SUR LES MOUCHES PARASITES. *Tome II. Calliphorides: Calliphorines (suite), Sarcophagines et Rhinophorines de l'Europe occidentale et méridionale. Recherches sur la morphologie et la distribution géographique des Diptères à larves parasites. Encyclopédie Entomologique, Série A., Volume XXI.*

By E. Séguy. Paul Lechevalier, Paris. 412 fr. (paper). 436 pp. 1941.

This volume is the second in the series of taxonomic studies on the parasitic flies of Western Europe. Thirteen years elapsed between the publication of the two parts and, consequently, revisions and corrections are included in the present volume. The first thirty-five pages list corrections to the Calliphorinae. The main body of the work is on the Sarcophaginae (197 p.) and Rhinophorinae (58 p.). Séguy has had access to many types and other valuable material and has redescribed many species. Drawings of entire flies, heads, male genitalia, etc. are well executed and should be of great value in simplifying the identification of species in these most difficult groups. In addition to descriptions, generic and species keys, and systematic bibliographies, there are notes on the biology and distribution for many species. The immature stages are still too poorly known to be treated systematically. In most cases the females, too, canot be identified with certainty. A bibliography of 32 pages and a full systematic index should be of great value to specialists in this field.

ROBERT MATHESON

SOUTH AMERICAN ZOO.

By Victor W. Von Hagen; illustrated by Francis Lee Jaques. Julian Messner, New York. $2.50. 182 pp. 1946.

Not since Sally Carrighar's *One Day on Beetle Rock* (Q.R.B. 20: 172. 1945) has a book about animals with the charm and the interest of this one come along. Like that book, this one owes a great deal to the striking series of woodcuts that embellish the text. The great southern continent is divided up into four "zoos," the Andes, the jungle, the pampas, and the islands; and the natural history of the most characteristic animals of each region is described in vivid prose that is suited to the "teen-agers" for whom the book was written, without being obtrusively written down to their level. The mammals and the birds receive most attention. The anaconda gets but a brief mention. There is somewhat more about the piranha and the electric eel, but nothing at all about the lungfish. Crocodiles, caymans, and the Galapagos tortoises and iguanas fare better than their relatives the snakes. But there is plenty to whet the appetite and vary the fare, so this is scarcely a criticism. It is enough to have met the condor, the spectacle bear, and the chinchilla; the tapir, sloth, and coati; the giant armadillo and the capybara; the toucan, rhea, and the birds of the guano islands; and many other equally remarkable creatures who live in that strange zoological garden to the south of us.

BENTLEY GLASS

FISHLORE: *British Freshwater Fishes. Pelican Books. By A. F. Magri MacMahon. Penguin Books, Harmondsworth, Middlesex, England.* 1s. (paper). 208 pp. + 8 plates. 1946.

This book is written by a layman for his brother laymen, and is intended to be a popular handbook for the freshwater and estuarine fishes of the British Isles. As such, it invites comparison with several similar books recently published in this country. It seems incredible that, with all vast output of pocket books in America, so few are devoted to natural history, and that there is nothing like this work among them. Several recent books on North American fishes are incomplete, erroneous, and often hack-written, and cost eight to twenty times as much as this little book although actually worth less. This book is well written, especially the introductory part on the general biology of

fishes, and well illustrated (although most of the plates seem to have been omitted from the copy in hand), and is more accurate than some of our own books by people with reputations as ichthyologists. The author freely admits his own shortcomings and refers the reader to more authoritative sources whenever necessary, which is a refreshing change from the seeming omniscience of some popularizers.

J. W. HEDGPETH

AMPHIBIANS AND REPTILES OF THE RIO CHUCUNAQUE DRAINAGE, DARIEN, PANAMA, WITH NOTES ON THEIR LIFE HISTORIES AND HABITS. *Bulletin of the American Museum of Natural History, Volume 86, Article 8.*

By C. M. Breder, Jr. American Museum of Natural History, New York. $1.60 (paper). Pp. 375–436 + 19 plates. 1946.

This is an account based on material collected twenty-two years ago. The species are listed and the area described in detail. An outstanding feature of the work is the attention paid to the embryology and breeding habits of certain frogs and turtles. There is a wealth of excellent illustrative material, both black and white drawings and photographs. A good deal of climatological data is included, and there are several informative maps. Breder, who is an ichthyologist, was aided by two herpetologists, Dunn and Bogert, on a number of matters concerned with the identification and nomenclature of specimens.

Under *Hyla underwoodi* there is a description of that commonly observed response of frogs in which a specimen perched on an investigator's hand maintains its head in a horizontal position despite considerable shifting and rotating of the hand. Breder is inclined to consider this a response to visual stimuli and does not mention the more likely possibility that the sensory impulses originate in the inner ear.

This paper appears to be a first class piece of work and should be of value to investigators interested in Central American herpetology and to those interested in the embryology of frogs.

ARNOLD B. GROBMAN

THE REPTILES OF MARYLAND AND THE DISTRICT OF COLUMBIA.

By Robert H. McCauley. Published by the author, Hagerstown, Maryland. $2.50 (paper). vi + 194 pp. + 16 maps + 16 plates. 1945.

Maryland has been ushered into the group of states boasting studies on their reptilian faunae by a very excellent report on the reptiles of the state and the District of Columbia. McCauley has done a creditable job, and his work should be useful for an extended period; it is already in its second printing.

This account follows the orthodox pattern that has become established for studies of this nature. After some general introductory material, there is an interesting historical summary of previous observations, a brief review of the physiography and climate of the area, an account of the life zones in the state, and several distributional lists of the reptiles. At this point, with the last three topics in retrospect, McCauley concludes that in Maryland the distributional limits of species of reptiles are more readily and clearly defined in terms of physiography than in terms of life zones. There then follows a systematic list of the forms involved, a discussion of the forms doubtfully assigned to the state, a brief account of the marine turtles, and a key to the species of reptiles inhabiting Maryland.

The individual accounts of species comprise the main body of the text. Each form is discussed under the following headings: common names, description, sexual dimorphism, range, distribution in Maryland, and habitat and habits. The concluding paragraph of the last section usually deals with the economic importance of the animal. Following the accounts of species are a bibliography, an index, the distributional maps, and a number of photographs, three to a page.

Some of the life history accounts are unusually good. There is a noteworthy discussion about several restricted areas inhabited by populations of *Natrix s. sipedon* with constant color variations. The economic importance of the diamondback terrapin is traced out, and an interesting table shows the wholesale price per pound for periodic intervals since 1880. Much of the observational data is quoted from the unpublished herpetological diaries of Father McClellan, who deserves a share of the credit for the excellence of these life history summaries.

McCauley calls attention to the fact that *Opheodrys aestivus*, a southern snake, lays eggs requiring a relatively long period of further incubation, whereas the eggs of *Opheodrys v. vernalis*, a northern snake, hatch in a much shorter time after they are laid. Concerning the latter he then concludes, "Probably the short incubation period is an adaptation contributing to the ability of this species to exist in northern habitats where the summer season is short." Were snakes warm-blooded, McCauley's conclusion would warrant attention, but since they are poikilothermic, it does not seem that the particular time during incubation (internal and external) when the eggs are laid is likely to be related, primarily, to either the length of the warm season or its temperature. Further to test the validity of McCauley's conclusion, Dr. Coleman J. Goin collaborated with the reviewer in constructing a

four-fold table to compare the numbers of ovoviviparous and oviparous species of snakes in Florida with those in Ohio, these states being selected as typical northern and southern states whose faunae were well enough known for our purpose. If the generalization were applicable, we would expect the ratio of ovoviviparous to oviparous to be high in Ohio, low in Florida. This is not the case; the difference is slight and is not significant; χ^2 is 0.74.

Why was this paper printed privately? It certainly betters the standards of many appearing in regular scientific journals and is not so "different" that a conservative editor would fail to accept it. One can readily see why it should *not* have been privately printed—it has many errors an alert editor would have caught: use lower case initials for *fasciatus* (p. 49) and *edwardsii* (p. 62), substitute "should not" for "cannot" (p. 102), delete "It is notable that" (p. 45), delete "DOR" from the list of institutions and individuals (p. 4), add page references in key to species (p. 27), etc.

The writing is good but occasionally overdone. Gastrosteges is used instead of ventrals. Anthropromorphic leanings are exhibited as *Terrapene* considers, *getulus* enjoys, *vernalis* is fond of hiding, and the like. The accounts would have been somewhat more cohesive if, under each species, reference had been made to the photographs and maps. The photographs are excellent, as are all those from Cornell, but have suffered from being reproduced on non-glossy paper. The base outline map used for the distributional figures could have been chosen more judiciously. Too much detail (e.g., the coastline of Chesapeake Bay) is shown, and the locality spots consequently do not strike the eye. The inset map designed to show the names of the counties is practically useless. Had other illustrations been scattered throughout the text, it would have been helpful, e.g., outline drawings along with the key.

The book is certain to be stimulating to those persons interested in Maryland reptiles and is most welcome on that score and many others. Yet the question does arise whether this is the best type of study for a doctoral student. State reports are probably best left for those investigators who have restricted allegiance, such as men in state museums, conservation departments, etc. Of more value to both the student and the science are studies of natural animal groups (usually genera) or natural areas (presumably, for reptiles, physiographic provinces). Cross sections through several adjacent physiographic provinces would likewise be of interest in comparative studies. It does not seem wise to confine efforts to an area whose boundaries have been determined solely by the vagaries of man's history.

ARNOLD B. GROBMAN

BIRDS OF THE PHILIPPINES. *The Pacific World Series By Jean Delacour and Ernst Mayr. With line drawings by Earl L. Poole and Alexander Seidel. The Macmillan Company, New York.* $3.75. xviii + 309 pp. 1946.

Another in the series of books on the natural history of the Pacific Ocean is the present volume on the birds of the Philippines. To quote from the foreword, "The original impulse for the preparation of the series came from the American Committee for International Wild Life Protection. This committee not only hoped but believed that a fuller understanding of the wonder and beauty of natural things by those in the Armed Services in the recent great war, as well as by their families and friends at home, would create a desire to protect and conserve the natural life of the islands, which, if once destroyed, can never be replaced." Mayr's recent volume, *The Birds of the Southwest Pacific*, Delacour's forthcoming *The Birds of Malaysia and Netherlands East Indies*, and the present volume will form a bird survey of considerable geographic scope. Although appearing too late for their original purpose, the value of these books to the student of birds is still of major importance, for nowhere else has so much information been assembled so compactly.

This member of the series begins with a few rather brief introductory remarks on the bird geography and habitats in the Philippines, and a few hints to the observer taken from Mayr's previous book. The list of species is arranged systematically. Each species is described by plumage, (occasionally by voice), size, and distribution. Sometimes there is a sentence or two on the habits and ecology of the bird or of a group of closely related species, but this type of information is very sparingly proffered, as so little is known about most of these birds.

There are field keys to many of the families, especially to the larger ones. Types of birds most likely to be unfamiliar to American students are illustrated by 69 line drawings. To conserve space, shore and sea birds of widespread distribution have not been elaborated upon, and in most cases are merely listed. Transients, however, are treated as fully as permanent residents. The distribution of subspecies on the various islands is also listed.

Palawan and associated islands, although politically a part of the Philippines, are faunistically Malaysian rather than Philippine. Birds from this region are therefore treated in a separate appendix. Those species (or subspecies thereof) already mentioned in the main portion of the text are merely listed, but endemic forms are fully described. The second appendix is a synonymy of genera used in the present volume with those used by McGregor and Hachisuka in their works on Philippine birds. To anyone desiring to compare these publications, the appendix will be a time-saver.

There is much to be learned about the birds of these islands; this book will provide the essential information for identification. From there on the observer will be on his own.

HENRI C. SEIBERT

MAMMALS OF NEVADA.

By E. Raymond Hall. University of California Press, Berkeley and Los Angeles. $7.50. xii + 710 pp. + 1 plate. 1946.

It seems unfortunate that this well-planned, elaborate and scholarly work has been held to the biologically irrelevant limits of state borders. Nevada is inhabited by 111 full species of living mammals, belonging to 6 orders and 23 families: the insectivores (2 families), bats (3 families), carnivores (5 families), rodents (8 families), hares, etc. (2 families), and even-toed ungulates (3 families). Half of all the species are rodents. On the basis of his extensive experience and long-continued field observations, the author calculates that the population of mammals in Nevada totals approximately a billion and a half individuals, a surprisingly high figure, considering the prevailing climatic and botanical factors, which call for such wide-spread adaptation to desert conditions. After very brief introductory chapters on the topography, climate, floral belts, life-zones, faunal areas, "factors responsible for geographic distribution and speciation," etc., the large bulk of this volume is devoted to a systematic and at times exceedingly detailed account of Nevadan mammals, including a check-list, a key to species, and even a hypothetical list of mammals "possibly occurring in Nevada of which satisfactory record is lacking." The professional mammalogist is given a painstakingly prepared, valuable catalogue of mammalian specimens collected in Nevada, with measurements, data on precise location, altitude, age, sex, coloration of pelage, subspecific characters, prevalence or density of occurrence, number of embryos per adult female, etc. Ecological data and the completion of life histories receive less attention than is customary in recent mammalogical treatises, since the author has been concerned first of all with problems of taxonomy and geographical distribution. Nevertheless, there are many significant new notes regarding mammalian behavior and the urgent problems of "game management." The volume includes a good glossary of technical terms, an extensive bibliography and a serviceable index, but no summary nor any conclusions.

This perfectly printed and generously illustrated volume (11 plates, 485 text-figures, many distribution maps) forms a welcome addition to the rapidly growing, remarkable recent literature that is fully recording the surviving mammalian fauna of North America with standards of detail rarely equalled for other continents. In the entire volume, however, no attempt is made to broaden the prevailing taxonomic methodology or to consider more than the all-too-few accepted characters or the somewhat crude statistical procedures.

A. H. SCHULTZ

THE ANIMAL A. B. C.

Photos by prominent photographers; rhymes by Sally Lee Woodall; drawings by Elmer Lasher. U. S. Camera Publishing Corporation, New York. $1.50. 55 pp. 1946.

As the title implies, this book is about animals, two for each letter of the alphabet being illustrated on each page, one by a sketch, the other by a photograph. In addition, a short verse relates the animals to the letter they accompany. The photographs are excellent, the sketches are too small and poorly displayed to attract attention, and the verses are strained, inaccurate (vide apes with tails!), and dull.

J. CUSHING

ECONOMIC ZOOLOGY

LES ANIMAUX PILLARDS ET DESTRUCTEURS DE L'ÉCONOMIE DOMESTIQUE: *Biologie, Morphologie, Parasitologie, Technologie. Ce qu'il faut savoir pour les connaître et les exterminer. Savoir en Histoire Naturelle, Volume XII.*

By E. Séguy. Paul Lechevalier, Paris. 60 fr. (paper). 250 pp. 1942.

Séguy, an eminent entomologist of the Paris Museum, has written this little popular guide to the pests of the French household in the form of an abbreviated encyclopedia. Insects, arachnids, crustaceans, mammals, insecticides, injuries, various control measures, hosts, etc., are all listed alphabetically in numbered paragraphs, with numerous cross references. Altogether there are 637 entries. For those needing additional information, there is a bibliography of seventy-three titles. The more common pests are illustrated by recognizable figures and, in addition, are characterized by some brief morphological and biological notes. Control measures are usually given in a separate entry.

ROBERT MATHESON

THE GARDENER'S BUG BOOK: *1,000 Insect Pests and Their Control.*

By Cynthia Westcott; illustrated by Eva Melady and

J. E. Edmonson. Edited by F. F. Rockwell. The American Garden Guild and Doubleday & Company, New York. $4.95. xviii + 590 pp. + 38 plates. 1946.

This book is rather unique in its make-up and in the method of presentation of the vast amount of information contained between its covers. It does not pretend to be a scientific textbook on insects and their control, but rather a popular account of the more common insect pests and the methods of controlling them which can be used in the garden. The first few chapters tell us how to use the book, about the various chemicals that are useful in the garden and their methods of preparation and application, as well as giving a brief account of some of the common spraying outfits. Following this comes a very brief chapter dealing with the classification of animals, so as to put the insects in their proper place. As the author sweetly reminds us, all bugs are insects and all insects are bugs; but she stretches this definition to include such garden pests as rabbits, dogs, squirrels, and their relatives, and I presume, she includes man himself.

Beginning with Chapter V, the insects are treated in alphabetical order under their common names, and certainly a wonderful arrangement is thus concocted. By much twisting and turning one is able to find almost anything; and when the desired information is found it is usually accurate and well told. In Chap. VI we have the plant hosts listed alphabetically, with a list of the common insect pests under each. By a combination of these two chapters and the index, the patient reader may be able to find the information desired.

The illustrations are well done, though the colored plates appear over-brilliant in tone. The line drawings are very characteristic and quite accurate. The book should prove very useful to the average gardener, and in the words of the editor (F. F. Rockwell), "No gardener can possess this book without having a far better garden than he could have had without it."

ROBERT MATHESON

LES COLÉOPTÈRES *des Denrées Alimentaires et des Produits Industriels Entreposés. Encyclopédie Entomologique, Série A, XXII.*

By P. Lepesme. Paul Lechevalier, Paris. 350 fr. (paper). 335 pp. + 12 plates. 1944.

In recent times much attention has been paid to the insect pests of stored products, particularly the Coleoptera. The present work is an excellent summary, with special emphasis on the biology and adult morphology of the beetles occurring in stored products throughout the world. Three hundred and ninety-nine species are reported in this treatise.

The first part, consisting of 239 pages, is a systematic review of the numerous species of pertinent beetles, belonging to 24 families. Keys are provided to the adults of all the families of beetles reported as occurring in stored products. Keys to species in the adult stage are given under each family. For the more important species there are detailed descriptions of adults and, occasionally, of immature stages. This is followed by a paragraph on distribution, biology, and injuries inflicted. Finally, there is a separate section on the life cycle. Very large, clear-cut original figures of adult beetles make recognition of the various species an easy task. In some cases figures of larvae and pupae are also given. Ten plates illustrate the types of injuries in various stored products, and two plates illustrate fumigating installations.

The second part of the volume is devoted to general considerations, particularly to the biological environment in stored products, food habits, geographical dispersal, life-cycles, and to predators and parasites (including a list of all known species). The sections on Injury and Control are very brief in comparison with the information on morphology and biology.

An extended bibliography of 32 large pages and separate indices to scientific and common names complete the volume.

ROBERT MATHESON

RESULTS OF TAGGING EXPERIMENTS IN CALIFORNIA WATERS ON THE SARDINE (SARDINOPS CAERULEA). *Fish Bulletin Number 61.*

State of California Department of Natural Resources, Division of Fish and Game, Bureau of Marine Fisheries, Terminal Island. Gratis (paper). 90 pp. 1945.

CATCH PER-UNIT-OF-EFFORT IN CALIFORNIA WATERS OF THE SARDINE (SARDINOPS CAERULEA) 1932-1942. *Fish Bulletin Number 62.*

By Ralph P. Silliman and Frances N. Clark. State of California Department of Natural Resources, Division of Fish and Game, Bureau of Marine Fisheries, Terminal Island. Gratis (paper). 76 pp. + 1 table. 1945.

While the sardine tagging experiment has resulted in a small actual percentage of recoveries, these recoveries can be used as a basis for estimating the total population. Because of the effect of migration, tag returns can not be used to measure the fishing and natural mortality. The average decrease of the sardine catch in pounds per-boat-week at all California ports from 1934-35 to 1941-42 is 48 per cent, and the average level of catch per-boat-week is lower for southern than for central California. About a third of Bulltin 62 is

given over to a detailed description of the methods of computation used.

J. W. HEDGPETH

ANIMAL GROWTH AND DEVELOPMENT

EINFÜHRUNG IN DIE PHYSIOLOGISCHE EMBRYOLOGIE. *Lehrbücher und Monographien aus dem Gebiete der exacten Wissenschaften. Reihe der Experimentellen Biologie, Band II.*

By F. E. Lehmann. Verlag Birkhäuser, Basel, Switzerland. S.Fr. 38.-(cloth); S.Fr. 34.-(paper). 414 pp. 1945.

This book was published in Europe during the last year of the war, almost simultaneously with Brachet's *Embryologie Chimique*. This remarkable fact is an eloquent testimony to the strength of the scientific spirit which has defied the tremendous difficulties that have beset the European centers of research during the last decade. Both books contain many references to experimental work done in European laboratories during the war. As few of these have been accessible outside of Europe, the books perform the valuable service of reestablishing our contacts with continental scientific activities.

Lehmann treats his subject in a rather unconventional way. The discussion is not centered around general topics or concepts such as induction, symmetry, or fields. Instead, the material is presented in the form of monographs of the development of two animal groups, the echinoderms and the amphibians. These two forms were selected for the obvious reason that they have been studied more thoroughly than any other, particularly with respect to the physiological and biochemical aspects of development. The author has further restricted the subject-matter by including only the "primitive development," up to the early pluteus larva and the late neurula, respectively. The later phases of organogenesis and growth are not treated.

The aim of the book is to present a story, step by step, of the early phases of development, a story that would be comprehensive in the sense that it would include and integrate all the information available from morphological, physiological, and biochemical investigations. Accordingly, the "primitive development" is subdivided into its natural phases, such as cleavage, gastrulation, etc., and each phase is discussed under three headings: normogenesis (normal morphogenesis, including morphogenetic movements), developmental mechanics, and physiology. Lehmann is of course aware that the time is not yet ripe for a true synthesis of morphogenetic and physiological data, largely because our information on the latter is very meager. However, he has been successful in his aim: to bring into focus the integrated and synchronized interplay of all developmental activities such as inductions, morphogenetic movements, and the cytological and metabolic changes which occur at any given phase in any given area. During the experimental analysis of these phenomena, it has been necessary to treat them more or less separately, and the analyst has often failed to resynthesize what he has taken apart. It is even more difficult for him to comprehend each stage of development as the result of the sum-total of all structural and physiological conditions prevailing in the preceding stages. Yet that is what an "understanding" of the developmental process, as a whole, amounts to. In this respect, Lehmann's *synopsis* is a valuable and necessary preliminary step to a future *synthesis*. From this point of view, certain experimental results are brought into the foreground, whereas others are barely touched upon. For instance, observations and experiments that show gradual shifts and changes in the responsiveness of a developing region to inductors or external agents ("phase-specificity"), and experiments which demonstrate the gradual restriction of regulative properties, are emphasized. Likewise, the phenomenon of the autonomous segregation of "fields" which, though poorly understood, must play an important role in progressive differentiation, is given due consideration.

The first subdivision of the book, which deals with *echinoderms*, begins with a brief chapter on their normal development. Its second chapter, that on developmental mechanics, is largely based on the work of Hörstadius. The third chapter, on echinoderm physiology, gives a detailed account of the gradient systems and their experimental modification, and of metabolic studies that are related to morphogenesis. The second, more extensive, subdivision, on *amphibians*, contains a section on the "plasma regions of the egg," one on "cleavage and blastula formation," one on "gastrulation and neurulation," and a general survey. Each section is subdivided into chapters on (a) normal morphogenesis, (b) experimental embryology, and (c) physiology. Some topics which are treated in detail deserve mention: the profound changes in the organization of the egg, both structural and physiological, following fertilization; the origin and stabilization of bilateral symmetry; the induction of the medullary plate; and the role of the nucleus in gastrulation and neurulation; there is also a special chapter on "organizer, teratomata, and neoplasms in amphibia."

The treatment of all topics is competent, thorough, and critical. Many tabulations of experimental results, partly devised by the author, and a sufficient number of black and white drawings in which over-schematization is happily avoided, help to clarify the subject-matter. The text, however, is written in a difficult style, and in a number of instances a shorter treatment would have been advantageous. Readability is further

impaired by the abundant use of technical terms, some of which have been coined by the author. It must be admitted that the terminology employed at present in experimental embryology is not concise, and that redefinitions are necessary. However, only a few of the newly introduced terms seem to contribute to the much-needed clarification. Terms like "phase-specificity" are welcome because they designate well-defined phenomena. Nevertheless, there is no need for a substitution of "(plastic) blastema" for the well-established "(morphogenetic) field," or for a new term, "organogenetic area (Areal)," to compete with "(field) district" (P. Weiss). Other terms,—such, for instance, as "Realisatorsystem" (which is defined as a "relatively unspecific complex of the metabolic apparatus which guarantees the normal processes of determinative and topogenetic changes") or "morphogenetischer Funktionszustand" and "morphogenetischer Funktionskomplex"—are dispensable in the opinion of the reviewer because they designate unanalyzed, complex phenomena which are not concisely definable.

Altogether, the book lives up to the high standards which the author has set up for himself. It cannot, however, very well claim to be an "introduction," for two reasons. It presupposes a considerable knowledge of experimental embryology; and it limits its scope to the discussion of only two animal groups. On the other hand, the specialist and the advanced graduate student will find in it a noteworthy and sound conception of primitive development, many stimulating ideas and suggestions, and much reliable information.

The book contains a glossary, author- and subject-indexes and, in addition, a detailed table of contents.

VIKTOR HAMBURGER

LES CHANGEMENTS DE SEXE. *L'Avenir de la Science, Number 23.*

By Étienne Wolff. Librairie Gallimard, Paris. 205 fr. (paper). 306 pp. + 24 plates. 1946.

The author, who is well known to American biologists through his contributions to the experimental analysis of chick development—the teratogenic effects of radiation, and induction of intersexuality by early hormone administration—has used the enforced "leisure" of five years spent as a prisoner of war to write a very engaging little book on the actual status of the problem of sex differentiation. Deprived of most library facilites, Wolff has made no pretense of covering the field completely. Relying largely on his memory, he has used facts and experimental data rather freely in illustrating the concepts which he had arrived at in his laboratory.

The preliminary part (75 pages) conveys some of the fundamental facts of morphological and genetical sex differentiation, including conditions of hermaphrodism. Emphasis is put on the primordial and potential bisexuality of the young and often even of the adult stages of all animals, which is the basis of natural and experimentally induced sex changes. The second part (55 pages) deals with the control of secondary sex characters and the chemical nature of the sex hormones.

The third part (72 pages) contains a summary of the author's own experiments and the outline of his theoretical interpretation of hormonal actions. In an opening chapter, Wolff discusses the "free-Martin" case and the experiments on amphibian parabiosis. Evaluating the antagonism between conjoined twins, he is inclined to attribute to the steroid sex hormones the role of exclusive controllers of all phases of sex determination. Full justification for such theoretical views he adduces from his own experiments with hen's eggs. Injecting above two micrograms of estradiol into the eggs about the fifth day of incubation, he induces the development of ovotestes in genetically male chicks. (Wolff gives due credit to the fact that the experiment was almost simultaneously reported also from other laboratories.) The fact of this experimental feminization is considered sufficient and safe ground for the conclusion that in the normal course of sex differentiation steroid hormones play the role of primary inductor substances. "All sexual differentiations are due to one single category of hormones, acting along the entire course of individual development, from the start of organogenesis to the adult stage." Furthermore, according to this new concept, "the first sex difference, which conditions all others, is a physiological, not a morphological one." The last conclusion is a little surprising, in view of the relatively broad consideration given to sex chromosomes in an earlier chapter. Wolff is too careful an observer to remain unaware that his sweeping generalizations run somewhat ahead of the facts. He knows that the feminization of his chicks is neither complete nor permanent, that a corresponding masculinization of ovaries with testosterone was never obtained, and that in mammals, early introduced sex hormones change only the secondary sex characters. But he seems to think of such contradictory and non-supporting evidence rather in terms of obstacles which will be overcome through continued research.

The fourth and fifth parts of the book review the available work on the genetics of intersexuality and on gynandromorphism. They will not fail to impress the reader with the high complexity of the specialized field of sex research.

EMIL WITSCHI

DEVELOPMENTAL ANATOMY: *A Textbook and Laboratory Manual of Embryology. Fifth Edition.*

By Leslie Brainerd Arey. W. B. Saunders Company, Philadelphia and London. $7.00. x + 616 pp. + 1 chart. 1946.

The fifth edition of this popular and widely used textbook differs primarily from the previous edition in that Part I, which concerns various topics of general development, has been extensively revised—in fact, it has been completely rewritten. The plan of organization of Part I and of the chapters comprising it is a distinct improvement over that of the former edition. Several chapters: Chapter VII (placentation), Chapter VIII (physiology of reproduction), and Chapter IX (experimental embryology) are well illustrated and interestingly written. For the inclusion of the material on experimental embryology the author is to be particularly commended. Although necessarily brief in its scope this material is a refreshing, finishing touch to Part I.

The remaining parts, II and III, have not been essentially changed, but a number of new and improved illustrations have been added. One minor criticism concerns the use of Fig. 486 (after Patterson) as an illustration of endoderm-formation in the chick. The endoderm is described in the text as originating by delamination, yet this illustration appears to indicate its origin by involution at the posterior edge of the blastoderm.

In general, from the point of view of the book as a teaching aid, this latest edition is an improvement over all preceding ones.

NELSON T. SPRATT, JR.

ANIMAL MORPHOLOGY

ART AND ANATOMY.

By Heidi Lenssen. Text edited by Lancaster M. Greene. Barnes & Noble, New York. $2.75 (cloth); $1.50 (paper). 80 pp. 1946.

"Into this volume the author has attempted to compress the essentials of human anatomy needed by the artist. Bearing in mind that a knowledge of anatomy, however useful, is but one of the manifold experiences important to the artist's work, the author has tried to exclude all nonessentials." In these words of the introduction are stated the aims of this volume. But it cannot be said, in the opinion of the reviewer, that the aims have been adequately realized. The 42 pages of original drawings (17 pages on the skeleton, 25 pages on the muscles) suffer greatly by comparison with many other published illustrations of human anatomy. Many of them are far too crude and inadequate. The 8 pages of text (2 pages on the skeleton, 6 pages on the muscles) are incomplete, inaccurate, and disorganized. It is unfortunate that they were not edited by someone familiar with more than the mere rudiments of human anatomy. By far the best feature of the book is the 22 pages of reproductions of anatomical studies by such "old masters" as Dürer, Michelangelo, Leonardo, Rembrandt, and Van Calcar (whose drawing from the *Fabrica* of Andreas Vesalius is ascribed to Vesalius himself), and the modern artists George Grosz and Walt Kuhn.

WILLIAM L. STRAUS, JR.

ANIMAL PHYSIOLOGY

MATHEMATICAL BIOPHYSICS OF THE CENTRAL NERVOUS SYSTEM. *Mathematical Biophysics Monograph Series, Number 1.*

By Alston S. Householder and Herbert D. Landahl. The Principia Press, Bloomington, Indiana. $2.00. ix + 124 pp. 1945.

Anyone interested in the development of a genuine theoretical biology would *a priori* be inclined to greet with pleasure a book with such a title as the above. This volume, however, is in certain vital respects a sad disappointment. The book is intended to summarize and bring up to date the work of the Rashevsky group on the theory of central nervous system function. The program initiated by Rashevsky proposes to analyse the behavior of organisms in terms of certain assumptions regarding the mode of action of individual neurones and the analysis of the behavior of various more or less complex networks of such neurones. The authors of this volume have been, since the original work of Rashevsky, among the outstanding contributors to this program. The topics considered, which include conditioning, learning, psychophysical discrimination, and the general characteristics of neural networks, are of undeniable importance. A particularly interesting section is Part 3, which represents a novel and ingenious application of propositional logic to the problem of inferring neural circuits from behavior, in contrast to the rest of the theory, which assumes circuits and deduces their behavioral consequences.

It is not possible to evaluate the results of the theory with any degree of finality. It would seem as if it accounts rather well for a fairly large range of phenomena. On the other hand, many of the comparisons of theoretical curves and experimental data indicate a rather naive attitude; much of the data probably would be fitted with more or less precision by any theory whose assumptions were not absolutely nonsensical. In the chapter on conditioning, for instance, figure 3 compares a theory of learning with data obtained by Gulliksen. Yet no mention is made of the fact that Gulliksen himself has presented a simpler theory of the learning process, resulting in mathematical expressions which superficially are quite different from that used by the authors, and which fitted the data equally well.

In the long run, the importance of such work depends upon its intelligibility to those people who would

benefit by reading it—in the present instance, neurophysiologists, psychologists, and general biologists. These are precisely the people to whom this book has been made almost hopelessly inaccessible by the mode of presentation used.

Not much of the mathematics is really difficult, although it is often more elaborate than the admittedly approximate character of the assumptions would warrant. But if the non-mathematician is to understand and use the theory, the ratio of discussion and interpretation to mathematics should be increased by at least a factor of ten. Moreover, the style of writing is one which, though natural to a pure mathematician, will inevitably be puzzling and repulsive to the mathematically uninitiated. The mathematics is so condensed and compressed, and the material is shot at the reader with such ferocious determined abstractness and formalism, that it would be a miracle if the contents of the book were ever to reach its intended readers.

It is easy to say that biologists must acquire a decent mathematical training and must overcome their present symbolophobia if progress in biological theory is to be made; it is also true. But biologists who are sufficiently receptive to mathematical theory to pick up and open a book on such a subject as this deserve something better than to have a bare mathematical skeleton thrust at them with a "take-it-or-leave-it" air. The authors should have modelled themselves more closely upon Rashevsky, whose two earlier volumes are very much more intelligible and attractive by comparison.

If it was the intention of the authors to put all the equations into a brief and compact form for reference, and later to write a book with which the biological reader could cope, most of the above criticisms would be irrelevant. In the absence of any hint of such an intention, however, it must be regarded as a definite setback for theoretical biology when two able and intelligent men write a volume upon some extremely significant material, the product of a good many years of painstaking research, in such a fashion that very few besides themselves are likely to have the courage to read it.

JOHN M. REINER

AGNOSIA, APRAXIA, APHASIA: *Their Value in Cerebral Localization. Second Edition Completely Revised.*

By J. M. Nielsen. Paul B. Hoeber, New York and London. $5.00. xii + 292 pp. 1946.

This second edition of Nielsen's well-known book beautifully presents these most difficult subjects. It includes a historical survey, a chapter on the normal gnosic, praxic, and phasic functions, the methods of examination in detail, and thorough descriptions of cases presenting the evidence for the author's conclusions. These conclusions are worth stating in their entirety:

1. The putamina have no function in language (this statement does not apply to the external capsules).

2. The minor cerebral hemisphere assumes the function of the major in language with great facility in some instances, with difficulty in others, and not at all in some persons.

3. The language function if partly destroyed does not usually transfer to the minor side in toto; the visual, auditory, or motor functions may be transferred separately.

4. An artificial writing mechanism may be formed on the minor side by training; when this happens the entire speech mechanism does not necessarily move to the minor side.

5. The major temporal lobe and the major occipital lobe may not be ipsilaterally located.

6. It is unsafe to lateralize a lesion on the basis of an aphasic manifestation alone.

WENDELL MUNCIE

HANDBOOK OF PHYSIOLOGY AND BIOCHEMISTRY. *Originally "Kirkes'" and later "Halliburton's." Thirty-eighth Edition.*

By R. J. S. McDowall. The Blakiston Company, Philadelphia. $6.00. xii + 898 pp. + 9 plates. 1944.

As recounted in a short foreword, this book is a lineal descendant of the *Physiology* of William Senhouse Kirkes (1823–64), which appeared first in 1848. Kirkes' book went through thirteen editions under various editors until 1896, when it was taken over by Halliburton and so extensively revised that the fourteenth edition of 1896 was to all intents and purposes Halliburton's *Physiology*. It is interesting to note that an American edition, with the chapter on the nervous system revised by Charles L. Dana, also appeared in this year, and that this and the subsequent American Revisions such as the fifth of 1904 (by Frederick C. Busch) and the seventh of 1910 (by Charles William Greene) followed the Kirkes rather than the current Halliburton text. Meanwhile Halliburton's *Physiology* flourished through seventeen editions and, since 1925, through seven more, under the new regime of Halliburton and McDowall. With the present volume, the *Physiology*, originally "Kirkes'" and later "Halliburton's", formally becomes "McDowall's". A textbook that has warranted a new edition every two and a half years through the first eighty years of its life, and somewhat more frequently during the remaining sixteen, scarcely needs any other accolade from the reviewer than an assurance that it is the same book, brought up to date but not militantly so, that medical students have studied with pleasure and profit for nearly a century.

H. R. CATCHPOLE

THE PROLONGATION OF LIFE. *A Robinson Foundation Publication. Essential Books.*

By Alexander A. Bogomolets; translated by Peter V. Karpovich and Sonia Bleeker. Duell, Sloan & Pearce, New York. $1.50. xviii + 98 pp. 1946.

This is a rather disappointing book, for it is not until one reaches the last two or three chapters that the author really forsakes generalities and the background of his subject, and commences to describe his own experimentation and the production of the famous ACS (anti-reticular cytotoxic serum). This is treated far too briefly to satisfy the curiosity of scientists outside of the U. S. S. R. To be sure, the book was not prepared for the scientific public, but for the great general body of Russian citizens, and that explains much.

It is clear, as one reads, that two men especially had to do with the formation of Bogomolets' ideas regarding aging. One of these was his teacher Metchnikoff, and the other was a famed Berlin physician of the early nineteenth century, C. W. Hufeland. From Metchnikoff, Bogomolets received the conception of the importance of the reticulo-endothelial system in maintaining health and youthfulness, although the idea that the phagocytes are the cause of the death of old cells he discarded. To Hufeland, Bogomolets acknowledges his indebtedness for emphasizing the importance of emotions, such as fear and boredom, in hastening ageing, as well as the idea that the natural life span of man is 150–200 years. Much of the book is filled with a discussion of the ideas about aging of these and other early scientists and doctors, and with a collection of records of longevity, including, of course, that of Parr and others from the eighteenth and nineteenth centuries, as well as a considerable number of records from contemporary Russia. These reports all appear to have been accepted at face value.

Coming to Bogomolets' own work, based on his theory of the aging and damage of colloids, i.e., cellular proteins, the first line of experiments dealt with colloidoclastic shock produced by blood tranfusions, which is said to occur even when donor and recipient are of the same blood type. The serum colloids clump and precipitate, after which they degenerate and are replaced by freshly synthesized proteins. The effect is presumably to rejuvenate the blood serum, and Bogomolets has advised blood transfusions to hasten recovery and convalescence in infectious diseases and to prevent recurrence of cancer after surgical removal.

A total of 10 pages is devoted to the discovery of the ACS serum and its uses. Metchnikoff first pointed out that sera might be prepared against particular types of cells (cytotoxic sera), and that by using small doses of such sera, cellular regeneration and, as a consequence, a degree of rejuvenation might be brought about. The practical difficulty was the determination of dosages and potency. Directions for the dilution of the serum are given, but the technical details of the entire process of serum production are unrevealed. ACS in strong doses was found to inhibit wound healing or the knitting of broken bones, but in small doses it exerts a stimulating action and hastens healing. Given in the first days of scarlet fever infection, in many cases it stopped the disease in 24 hours (no details). Following surgical removal of cancer, ACS was reported to reduce considerably the percentage of recurrence, within three years, of cancer of the stomach (no figures). In short, ACS offers great hope for the prolongation of life.

Bogomolets died in 1946 at the age of 65.

BENTLEY GLASS

THE MODERN METHOD OF BIRTH CONTROL. *New Edition.*

By Thurston Scott Welton. Grossett & Dunlap, New York. $1.49. xii + 159 pp. + 1 chart. (1946).

Here is a complete and inexpensive handbook for the Ogino-Knaus system, with numerous colored charts for all the variants and vagaries of the menstrual cycle, complete with a transparent "calendar-wheel" that is sure to appeal strongly to everyone with a leaning toward astrology. There is an extremely simple discussion of human reproductive processes, and a summary of the position of the Roman Catholic Church on contraception. If one can find the right chart, a matter involving the ability to count and to mark a calendar, satisfaction is guaranteed, provided one expects the right thing. In any event, the "Modern Method" is maybe as effective as most others, and considerably cheaper, even with the cost of this book reckoned in.

BENTLEY GLASS

BIOCHEMISTRY

TEXTBOOK OF BIOCHEMISTRY. *Fourth Edition.*

By Benjamin Harrow. W. B. Saunders Company, Philadelphia and London. $4.25. xiv + 592 pp. 1946.

The fourth edition of Harrow's *Textbook of Biochemistry* continues to uphold its standard of clarity and readability. Biologists will find this book a readily available source of information on problems of a biochemical nature, and a relatively up-to-date account of the status of the knowledge and thinking of their biochemical colleagues.

Certain additions and rearrangements have been made in this edition. The treatment of the chemistry of the sugars has been modernized by making their cyclic structure the basis of the discussion. Important

advances in the various fields of both pure and applied biochemistry have found their way into various chapters of the book. Of these we may mention such things as the recent findings on the antagonistic actions of metabolic analogs, mechanism of action of sulfanilamide, antibiotic substances such as penicillin and streptomycin, as well as others.

One relatively novel innovation of the present edition is the expansion of the appendix to include proofs for the structure of certain important compounds, as well as a discussion of the property of solutions. The synthesis and preparation of biochemical compounds of interest are also included here.

The section on polysaccharides, although slightly revised with respect to the structure of starch, still remains, in the opinion of this reviewer, relatively inadequate. This is particularly so when one considers the established biologic importance of polysaccharides as immunologically specific agents. Furthermore, recent research on these compounds has provided the one available example of an almost completely understood and defined mechanism for the synthesis of a complex biological compound. A more thorough discussion of the recent work of the Coris on glycogen could have exhibited a principle of biological synthesis which is probably basic and widespread.

The discussion of the metabolism of carbohydrates is more adequate than that of previous editions. However, here again a splendid opportunity was missed to discuss general principles that could act as unifying concepts for the student and reader. I refer particularly to the absence of a thorough discussion of the phosphate bond mechanism whereby cells can trap the energy of oxidation in energy-rich bonds which can then be used for other energy-requiring processes.

The additions suggested above could conceivably increase the usefulness of an already valuable book. However, with or without them, it can be highly recommended both as a text for students and as a source of information for biologists.

S. SPIEGELMAN

ADVANCES IN PROTEIN CHEMISTRY. *Volume II. Edited by M. L. Anson and John T. Edsall. Academic Press, New York.* $6.50. xiii + 443 pp. 1945.

Dealing as it does with a class of compounds of unique interest to biologists, it is inevitable that the series *Advances in Protein Chemistry* should be warmly received by biological workers. The second volume maintains the high standard of thoroughness and usefulness initiated by the first. A particularly welcome feature, for which the editors are to be highly congratulated, is the avoidance of the bibliography-listing style common to some other review volumes. The articles are both informative and critical, permitting the uninitiated reader to examine the conclusions of the experts in the field on the validity and utility of the data and methods presented.

The greater part of the present volume is devoted to problems of the structure and chemical composition of proteins as distinguished from their biological function. The first chapter deals with the analytical chemical methods employed in investigations into the composition of proteins. In addition to the more classical procedures, the authors, Martin and Synge, include useful descriptions of more recent developments such as isotope dilution, and chromatographic and spectrophotometric procedures. Biologists who seldom have very large quantities of materials at their disposal for analysis will be particularly interested in the recently developed partition methods. With one of these, the 2-dimensional strip procedure, clear separation of over twelve of the constituent amino acids can be obtained with less than 0.4 mg. of protein.

Sneli, in the second chapter, describes the microbiological methods for the assay of amino acids. Individual assay methods are discussed, as well as the criteria for establishing reliability. Cannon surveys the work on the relationship of protein metabolism to antibody production and resistance to infection. Recent work by the Yale school on the role of lymphocytes in this process will undoubtedly affect the viewpoint of future reviews on this subject. Fankuchen contributes a discussion on the use and future of x-ray diffraction studies of protein structure in his usual excellent and succinct style. Anson's survey of protein denaturation and the recent contributions in this field will be of particular interest to biologists.

Other topics covered include the amino-acid composition of food proteins, terminal amino acids in peptides and proteins, the enzymologically important copper proteins, glycoproteins, wheat gluten, and the reactions of formaldehyde with amino acids and proteins.

S. SPIEGELMAN

THE AMINO ACID COMPOSITION OF PROTEINS AND FOODS. *Analytical Methods and Results. By Richard J. Block and Diana Bolling. Charles C. Thomas, Springfield, Ill. and Baltimore.* $6.50. xiv + 396 pp. 1945.

The work of the authors themselves, and a digest of nearly seven hundred papers from the literature, forms the basis of this practical manual. It deals principally with chemical analysis, by the use of specific precipitants and reagents. Methods, some of which through the years have become encrusted with modifications, are succinctly presented in their most up-to-date guise, and the authors' comments on their use and limitations are particularly instructive.

GEWINNUNG DER HÖHEREN FETTSÄUREN DURCH OXYDATION DER KOHLENWASSERSTOFFE. *Moderne fettchemische Technologie, Heft 2.*

By F. Wittka. (Johann Ambrosius Barth, Leipzig); J. W. Edwards, Ann Arbor, Michigan. $4.15. vi + 167 pp. (1940); 1945.

A short technical manual of fatty acid production from natural and synthetic hydrocarbons. References are drawn largely from the patent literature. Soap manufacture is the primary interest, and only brief mention is made of the production of edible fats.

ORGANISCHE KOLLOIDCHEMIE. *Die Wissenschaft, Band 93.*

By Hermann Staudinger. (Friedr. Vieweg & Sohn, Braunschweig); J. W. Edwards, Ann Arbor, Michigan. $4.50. viii + 243 pp. (1941); 1945.

It is obviously of limited value to review in 1946 a book which appeared in 1941, particularly because the field of organic colloid chemistry has made such rapid progress during the last ten years. From the point of view of today the content of the book is almost obsolete, as evidenced by the fact that such important polymers as polyethylene, polyvinylchloride, polyvinylacetate, polyvinylalcohol, polyacrilonitriles, polysilicones and many others are not even mentioned. To be fair, it is therefore necessary to discuss the value of the book from the point of view of our knowledge as of 1941.

Taking this approach, it can be reported that the three final chapters give a very lucid and concise description of the classification of organic and inorganic colloids, with particular emphasis on organic high polymers. The fourth and fifth chapters are, in the reviewer's opinion, the real core of the book, as they present the structural details of organic polymers and the shape of their particles in solution in an adequate and—for 1941—up-to-date manner. Their content is mainly organic chemical, and the high quality of presentation of this subject will surprise no one who is familiar with the work of Staudinger.

The following chapters on viscosity, swelling, osmometry, etc., mainly of physical chemical nature, are not of quite the same high standard; they contain a series of somewhat confused and even inaccurate statements, together with a number of oversimplifications, which even in 1941 were already in obvious contradiction with the then known experimental facts.

It would be very desirable if this book could be rewritten and if more thoroughness and care could be devoted to the discussion of the size and shape of polymer molecules in dilute solutions and to an up-to-date presentation of all the interesting relationships which have been revealed recently by the application of numerous physical methods.

I. FANKUCHEN

SCIENTIFIC PROGRESS IN THE FIELD OF RUBBER AND SYNTHETIC ELASTOMERS. *Advances in Colloid Science. Volume II.*

Initiated by the late Elmer O. Kraemer; edited by H. Mark and G. S. Whitby. Interscience Publishers, New York. $7.00. xl + 453 pp. + 1 plate. 1946.

The last few years have seen a disturbingly large number of new books entitled "advances of this" and "currents of that." The reviewer would not have had occasion to use the word 'disturbingly' if all such volumes were of the quality of this one. The editors have chosen their authors with care and have wisely limited the number of chapters to only nine. This has permitted more extensive treatment of many of the subjects than is usually found in such volumes. The editors have also included a biography of E. O. Kraemer, whose premature death in 1943 removed from the field one of its real pioneers. In a sense this volume is a fitting memorial to a great man.

The reviewer finds those chapters he is interested in particularly good. Wood, in discussing crystallization phenomena, compactly presents both the pertinent ideas and data in this field. Bunn has written a thoughtful and provocative chapter on the x-ray studies of rubber-like materials. It contains much meat for workers in x-rays in fields other than rubber research. Other chapters discuss second order transition effects, the kinetic theory of rubber, elasticity, etc. I like this book.

I. FANKUCHEN

ENZYMES *and Their Role in Wheat Technology. American Association of Cereal Chemists Monograph Series, Volume I.*

Edited by J. Ansel Anderson. Published for American Association of Cereal Chemists by Interscience Publishers, New York. $4.50. x + 371 pp. 1946.

This represents apparently the first of a series of monographs sponsored by the American Association of Cereal Chemists and is primarily designed to serve as a source of information of interest to its members. The particular purpose of the present volume is to cover the parts of the field of enzymology of interest to cereal chemists. This book illustrates well the impact of technological demands on the biological sciences and the impetus they give to certain varieties of research. To those uninformed about this field it will come as some surprise to note how extensive has been the use of modern enzymological research in the technology of wheat and its by-products.

The general plan of the book alternates theoretical with practical chapters. Following a general introduction into the chemistry of enzymes, a chapter is devoted to a discussion of the amylases, and the third chapter considers the problem of applying the amylases

to milling and baking technology. The same plan is followed with esterases, in which are included both the lipolytic enzymes and phosphatases. The oxidizing enzymatic systems are authoritatively discussed by E. S. Gutzman Barron. This is then followed by a chapter dealing with the problem of oxidizing enzyme systems of wheat and flour, by Sullivan. The general properties of proteases are discussed by Ball and Kies, and their application in baking by Hildebrand. The mechanism of alcohol fermentation is described by Werkman, and the book concludes with a chapter on yeast fermentation, in relation to the baking industry, by Atkin, Schultz, and Frey.

While it is apparently the hope of the editor that this book, and possibly succeeding members of the series, might prove useful to many persons other than cereal chemists, it seems doubtful that this will turn out to be the case. This present book actually deals with some very broad problems in enzymology. However, those chapters which deal with the more general aspects and therefore, which might appeal more widely, have been very well covered—in some instances by the same authors—in review volumes normally seen and purchased by biochemists and biologists.

S. SPIEGELMAN

LABORATORIUMSBUCH FÜR DEN LEBENSMITTELCHEMIKER. *Fourth Edition.*

By A. Beythien. (Theodor Steinkopff, Dresden and Leipzig); J. W. Edwards, Ann Arbor, Michigan. $15.00. xxiv + 624 pp. 1944.

Three editions of this text have appeared in Germany since 1939, and the present volume is a reprint of the last, that of 1944. The literature appears to have been brought up to 1940, at least, and directions are brief and to the point. Besides dealing with methods and computations for the analysis of thirty-five groups of foodstuffs, there is a varied section that includes the analysis of utensils, paper, soap, etc., and another on inorganic and organic poisons, including certain alkaloids and organic acids.

ANTIBIOTICS. *Part I: Microbiological; Part II: Pharmacological. Annals of The New York Academy of Sciences, Volume XLVIII, Art. 2.*

By Werner W. Duemling, Garfield G. Duncan, William H. Feldman, J. W. Foster, A. Hervey, H. C. Hinshaw, M. J. Johnson, F. Kavanagh, A. Kleinman, Hans Molitor, Edwin Pulaski, Geoffrey Rake, Kenneth B. Raper, D. M. Reynolds, Arthur P. Richardson, W. J. Robbins, H. Robinson, A. Schatz, Selman A. Waksman, and H. B. Woodruff. The New York Academy of Sciences, New York. Price? (paper). Pp. 31–218 + 9 plates. 1946.

This special number of the Annals contains a series of papers presented before the Conference on Antibiotics held by the Section on Biology of the New York Academy of Sciences in January 1946. The contents are divided into two sections, (I) microbiological, and (II) pharmacological.

Part I is introduced by a general discussion of the subject by Waksman with some interesting historical information regarding the development of the basic concept of antibiosis. The development of improved penicillin-producing molds by Raper reviews the work of many workers, leading to the positive identification of Fleming's mold and the subsequent analysis of thousands of cultures belonging to the *Penicillium notatum—chrysogenum* group. He then covers the establishment of the general principles that the capacity to produce penicillin as a metabolic product represents a group characteristic rather than a strain characteristic; that different members of the group vary greatly in their capacity to produce penicillin; and that particular strains are especially suited for certain types of production.

In discussing the metabolism of penicillin-producing molds, M. J. Johnson describes the studies carried out to determine the best culture conditions for high penicillin yield. For a given culture, yield is a function of such variables as pH, available oxygen, rate of carbohydrate oxidation, and available combined nitrogen. The details of the chemical changes taking place in the media in the process employed for the industrial production of penicillin are given. Robbins, Kavanagh and Hervey briefly review the studies made with the basidiomycetes as possible sources of antibiotic substances. This group of fungi is said to contain some 30,000 species, of which only a few have been investigated from this standpoint. It would appear that we are just beginning to tap a vast reservoir of possible antibiotic producers. The authors describe the preparation of substances which at considerable dilution inhibit the growth of certain bacteria, but no substance as active as penicillin has been discovered in this group as yet. In similar vein is the chapter by Waksman, Schatz, and Reynolds on the production of antibiotic substances by actinomycetes. In this group several distinct antibiotics have been isolated. Some, namely, actinomycetin, micromonosporin, mycetin, and actinomyces lysozyme have been partly purified, whereas actinomycin, proactinomycin, streptothricin, and streptomycin have been isolated and crystallized. Foster and Woodruff discuss the antibiotic substances from bacteria and point out the need for scientific appreciation of this field. They stress the importance of more exact chemical identification of the antibiotic substances reported in the literature. The possible mode of action of antibiotics is discussed, and the re-

searches with *Bacillus brevis* and the chemical and antibacterial properties of gramicidin and tyrocidine are reviewed by these authors.

Part II concerns the general pharmacology and clinical experiences with the antibiotic agents. Hans Molitor reviews the toxicity experiments with streptothricin and streptomycin. The presence of a histamine-like compound in streptomycin as a contaminant, and the presence of a highly toxic factor or factors, not related to the antibiotic potency, illustrates the importance of knowledge of this character. The author concludes that on the basis of its pharmacological and toxicological properties and its extraordinary chemotherapeutic activity, streptomycin is a safe chemotherapeutic agent. However, streptomycin, unlike penicillin, is active pharmacodynamically as well as its impurities. Photographs of tissue sections and of blood pressure tracings are included. Streptomycin and streptothricin absorption, excretion, and chemotherapeutic properties are reviewed by Robinson. A complete list of the literature on this problem is presented. Those interested in the treatment of bacterial infections with the antibiotics will find this chapter of interest. The author stresses the factors involved in preventing the development of acquired resistance under therapy.

The pharmacology of penicillin, reviewed by Rake and Richardson, combines in one chapter of 31 pages practically all the available information on the subject at the time of publication, a collection that is unique at this time. The data are unfortunately too extensive to discuss here. The authors stress the importance of designating the character of the penicillin employed in experimental work and use "penicillin" in quotation marks to indicate its variable composition of F, K, G, and X forms.

Three chapters of clinical interest follow: one by Hinshaw and Feldman on Streptomycin in Treatment of Clinical and Experimental Tuberculosis; one by Pulaski, Kleinman, and Duncan on Some Considerations of the Clinical Application of Streptomycin; and the third by Demling on Clinical Experiences with Penicillin in the Navy.

As indicated in the first chapter, the purpose of these papers is not only to summarize our present knowledge of antibiotics and their application, but to call attention to the problems that still await solution. This collection of articles seems to fulfill these requirements in a scholarly manner.

C. JELLEFF CARR

ACETANILID. *A Critical Bibliographic Review. Monographs of the Institute for the Study of Analgesic and Sedative Drugs, I.*

By Martin Gross; with an introduction by Howard W. Haggard. Hillhouse Press, New Haven. $3.00. xviii + 155 pp. 1946.

This volume is the first in a series of critical reviews of the literature on analgesic and sedative drugs. The collection and evaluation of the investigative studies and clinical reports on acetanilid should do much to clarify the controversies that have been precipitated by the introduction of this drug into therapeutics. The emphasis is placed on the reported toxicity of acetanilid, and 45 pages are devoted to a discussion of acetanilid poisoning. The treatment of the subject has been criticized by some reviewers as too critical of clinical work tending to show potential dangers from acetanilid, while little fault was found with work tending to show the opposite. In the opinion of this reviewer, Gross has fairly and judiciously presented his subject. The book is a valuable compilation of the literature on this drug. The cross references at the end of each chapter and in the general bibliography are excellent and represent a tremendous amount of painstaking labor. Pharmacologists and other students of the subject will find this volume very useful.

C. JELLEFF CARR

MODERN DEVELOPMENT OF CHEMOTHERAPY. *Monographs on the Progress of Research in Holland During the War, Number 4.*

By E. Havinga, H. W. Julius, H. Veldstra, and K. C. Winkler. Elsevier Publishing Company, New York and Amsterdam. $3.50 (paper). xii + 175 pp. 1946.

As indicated in the foreword by the editors of this series, the purpose of this publication is to show the world that scientists in the Netherlands remained active during the five years of German occupation. This little monograph, published on V-E Day, May 8, 1945, seems to fulfill the wishes and the spirit of its editors.

The major portion of the text is devoted to a discussion of the mechanism of action of the sulfonamides and para-aminobenzoic acid. A lucid description of the characteristic action of sulfanilamide on bacteria, a well-defined and fundamentally different action than that possessed by any previously known anti-bacterial substance, is set forth in chapter II. As the authors point out, this phase of the subject is the principal point of interest in this monograph, and "is a justification of the purely experimental and scientific studies on sulfanilamide action *in vivo*, sometimes looked upon by the clinician as a laboratory phantasy." Thirty pages are devoted to a description of the chemistry of related derivatives of the sulfonamides and their trials *in vivo* and *in vitro* as anti-bacterial compounds. The

remainder of the section is concerned with pharmacological, immunological, and clinical investigations of the sulfonamides.

Of considerable interest is the final chapter, which describes the discovery, isolation, and identification of an antibiotic substance from *Penicillium expansum*, named "expansine." This material has been assigned a chemical structure which later proved to be identical with that of patuline, clavacine, and claviformine. All this was accomplished without a knowledge of the activities of the American and English workers, and it is casually mentioned by the writer that "part of the investigations were hampered by the impossibility of carrying out analyses, caused by the lack of sufficient supplies of gas and electricity."

The volume is well written and except for occasional quaint expressions and spellings, such as "alcaline," the text is free from errors. As a demonstration of the indomitable spirit of the scientific mind this little book is recommended to all.

C. JELLEFF CARR

ADVANCING FRONTS IN CHEMISTRY. *A series of lectures sponsored by Wayne University under the direction of Neil E. Gordon, Chairman, Department of Chemistry. Volume II: Chemotherapy.*

Edited by Wendell H. Powers. Reinhold Publishing Corporation, New York. $3.50. 156 pp. 1946.

This collection of lectures, delivered at Wayne University in 1945, contains chapters each written by a different author, and the scope of the book is indicated by the chapter titles. W. H. Feldman reviews "Chemotherapy in Experimental Tuberculosis," in a discussion that deals largely with the researches of the author and his associates. F. H. Blicke, writing on "Antispasmodics," represents the changing interpretation of the word chemotherapy, and provides an example of the ingenious capacity of the chemist to follow leads furnished by natural compounds and to prepare new antispasmodics of superior qualities. A general outline of the theories of mechanism of action of the sulfonamides is contributed by E. H. Northey. H. S. Mosher, in discussing "The Antimalarial Problem," deals with the chemistry of the compounds used in the treatment and prophylaxis of this disease. "Organometallic Compounds as Chemotherapeutic Agents," by C. K. Banks, outlines the uses of compounds of arsenic, antimony, bismuth, gold, mercury, and silver in infectious conditions. "Past and Present Needs in Chemotherapy of Parasitic Diseases," by W. H. Wright, summarizes, with considerable duplication, the preceding discussions. The references at the end of each chapter appear to be adequate.

C. JELLEFF CARR

MICROBIOLOGY

INSECT MICROBIOLOGY. *An Account of the Microbes Associated with Insects and Ticks with Special Reference to the Biologic Relationships Involved.*

By Edward A. Steinhaus. Comstock Publishing Company, Ithaca, New York. $7.75. xiv + 763 pp. 1946.

In this weighty compendium, Steinhaus has attempted to bring together all available information on the interrelationships of insects and microorganisms—an enormous undertaking for one man, necessitating as it must a knowledge of entomology, bacteriology, protozoology, mycology, and immunology. The first five chapters, comprising almost half the book, deal in detail with the associations of insects with eubacteria, rickettsiae, and symbiotic microorganisms presumed to be of bacterial or rickettsial nature. This is followed by somewhat briefer discussions of the yeasts, fungi, spirochaetes, viruses, and protozoa associated with insects, a special chapter being devoted to the protozoan fauna of termites and the nature of this consortium. The text concludes with an account of immunity in insects and a chapter on methods and procedures. There are ninety pages of references, as well as author and subject indices. Good illustrations are provided throughout, and the book is remarkably free from typographical errors.

The reviewer is to some extent disarmed by his realization that no contemporary biologist could be expected to treat this vast mass of data, drawn from so many divergent fields, with real critical authority. Nevertheless, one cannot help feeling that the subject matter could have been presented in less indigestible form. Due to the approach adopted, the different *kinds* of insect-microbe relationships, each of which may of course extend over several microbial groups, are never clearly brought out. One looks in vain for general discussions on diseases of insects, mutualistic relationships between insects and microorganisms, and microorganisms as insect food supplies. These broad topics are split up and dealt with piecemeal under the different categories of microbial life. Another feature which makes the book difficult to read is the author's practice of cataloging unimportant information. Thus chapter XI contains in the text a list 16 pages long of the genera and species of protozoa found in termites, accompanied by the names of the host species but unrelieved by any descriptions. Only a protozoologist completely *au fait* with the complexities of the hyper- and polymastigotes could find this of interest or utility. My patience was also sorely tried by chapter III, entitled "Specific bacteria associated with insects," which is a catalogue, extending over 150 pages, of specific bacterial names (without descriptions), followed by brief notations on the insects with which these forms are allegedly associated. Many of the listed organisms are clearly either of no real significance

in connection with insects or so inadequately known as to be unrecognizable on fresh isolation. If this chapter had been confined to *bona fide* insect parasites and pathogens properly characterized, it would have served a far more useful purpose.

A point which strikes one very forcibly after reading this book is the paucity and triviality of the available information on the relationships between bacteria and insects, except in connection with problems of medical importance. We are still largely in the dark concerning such matters as the nature and function of the normal bacterial flora, the use of bacteria as food by insects, and possible symbiotic relationships between the two groups. This appears all the more remarkable because a good deal of fascinating information on fungal and protozoan relationships to insects has been accumulated, often by the simplest of observational methods. One need only mention the striking association between fungi of the genus *Septobasidium* and scale insects, the cultivation of specific fungi for food by wood-boring beetles and ants, and the termite-flagellate consortium. I believe that the root of the trouble lies in the unimaginative rigidity of the bacteriological approach, fettered by the convention of "standard methods." If the bacteriology of insects is to be studied, as Steinhaus recommends in the chapter on methods and procedures, by plating on nutrient blood agar or similar substrates, growing the isolated bacteria in standard differential media, and then attempting identification with the aid of Bergey's *Manual*, our present state of ignorance is likely to persist. A much more subtle and elastic approach is required to prevent the subject from being merely a dreary cataloging of random isolates, whose chief distinction is their ability to proliferate on an arbitrarily chosen list of media devised for the identification of certain bacteria occurring in the gut of *Homo sapiens*. The study of each group of bacteria demands the elaboration of a special methodology, and so-called "standard methods" are useful only when used with the group for which they were developed, namely, the *Enterobacteriaceae*.

Two rather important omissions were noted. In the discussion of polyhedral virus diseases of insects, no mention was made of the work done in recent years by Bergold and Desnuelle and their respective collaborators on the virus of silkworm jaundice; this is perhaps due to the unavailability of European journals at the time when the book was completed. Less understandable is the failure to discuss Hungate's beautiful work on the nutrition of *Zootermopsis* and his conclusions concerning the biochemical basis of the termite-protozoan relationship, an omission which greatly reduces the value of the chapter dealing with this subject.

ROGER STANIER

HEALTH AND DISEASE

AUTOPSY DIAGNOSIS AND TECHNIC. *Second Edition, Revised and Enlarged.*

By Otto Saphir; foreword by Ludvig Hektoen. Paul B. Hoeber, New York and London. $5.00. xxiv + 405 pp. 1946.

This pocket-sized volume is a comprehensive and authoritative guide to the technic of performing autopsies on human bodies. In addition it lists and very briefly discusses the macroscopic structural changes produced by disease and injury. This manual will be helpful to advanced medical students and to physicians in connection with post-mortem examinations. It presupposes a thorough knowledge of normal human anatomy and forms an addition to, though not a substitute for, textbooks of pathology. Only that one autopsy technic is presented which the author has found most useful in his own extensive experience. Throughout the book there are numerous, brief, and somewhat arbitrarily selected references to teratological conditions, which take it for granted that the reader is familiar with normal development and with the causes of developmental defects.

This second edition contains a number of new or enlarged chapters. The diseases of the breast have received special attention and outlines of the anatomically demonstrable consequences of vitamin deficiencies and of many tropical diseases have been added. A further new chapter deals with autopsies of stillborn children. The book ends with lists of average weights and dimensions of human organs. These summarized data, without any reference to race, body size, number of individuals examined, etc., are of quite limited value. The index is adequate, but nearly all of the 69 illustrations are inexcusably crude and often unnecessarily large.

A. H. SCHULTZ

HEALTH AND FITNESS.

By Florence L. Meredith. D. C. Heath and Company, Boston. $2.00. x + 325 pp. 1946.

YOUR HEALTH AND SAFETY. *Revised Edition.*

By Jessie Williams Clemensen and William Ralph LaPorte. Harcourt, Brace and Company, New York and Chicago. $2.12. viii + 592 pp. 1946.

These two textbooks designed for use by high school students are well made up, written, and illustrated. They cover many aspects of human physiology, personal hygiene, and public health, and present recent advances in control of disease.

The book by Meredith is particularly attractive because of its many cartoons, as well as graphs and pictures. The textual content is very simple, so that most of it could be used at the junior high school

level. So far as it goes, it is well done. In the preface, Florence Meredith states that the book "includes information applicable to situations the student is quite likely to meet soon after he leaves high school." However, the anatomy is of that practically neuter gender so popular in high school science texts. The physiology of the reproductive system is not considered, although there is a chapter on "Choosing a Mate" in the section on mental hygiene. Another serious defect is omission of the venereal diseases from the discussion of communicable diseases.

The text by Clemensen and LaPorte contains considerably more information on most subjects, including physiology, although very little attention is given to reproduction. Both syphilis and gonorrhea are included in the consideration of disease prevention, and the relation of syphilis to cardiovascular and mental diseases is pointed out. At the end of each chapter, there are not only suggestions for student activities, but also references, which encourage the student to widen his knowledge by means of the school or town library. There is also a glossary of terms and lists of literature, motion pictures, and other information in the appendix.

HARRIETTE D. VERA

FIVE IN THE FAMILY. *Health and Personal Development Book C (For Grade 3): Curriculum Foundation Series.*

By Dorothy Baruch, Elizabeth Montgomery, and William S. Gray. Illustrated by Miriam Story Hurford. Scott, Foresman and Company, Chicago. 96 cents. 192 pp. 1946.

A family of two boys and their older sister are presented in various aspects of their daily life, between the older boy's sixth and seventh birthdays. There are many good colored illustrations, at least one on each page, that make the book interesting even to younger children than those in the story. The narration covers such events as a birthday party, a visit to the dentist, the girl's cold, and the building of a playground. Cleverly incorporated are simple suggestions on safety in the home, the achievement of good health, and various interesting ways to have fun at constructive things. The style is simple and attractive and should appeal to young readers.

J. CUSHING

THE AMERICAN HOSPITAL. *Studies of the New York Academy of Medicine Committee on Medicine and the Changing Order.*

By E. H. L. Corwin. The Commonwealth Fund, New York. $1.50. xvi + 226 pp. 1946.

The medical and economic importance of hospitals has immensely increased during the last few decades. Hospitals now form one of the twelve major "industries" of this country. At least one in ten persons went into a hospital as an inpatient in 1943. General hospitals, owning 40 per cent of all the beds, admit over 90 per cent of all the patients. Voluntary hospital plans now have 21 million members. Criticism in the hospital field has been directed primarily against limited facilities in certain regions or for certain classes of the population, and against the methods of staff appointments.

For everyone looking for information on the hospital situation in this country, as to its strong and its weak points, its problems and its future, the author has presented in 200 pages an extemely full, reliable and equitable picture, which in spite of its factuality makes most fascinating reading.

ERWIN H. ACKERKNECHT

THE CONTROL OF VENEREAL DISEASE.

By R. A. Vonderlehr and J. R. Heller. Foreword by Thomas Parran. Reynal & Hitchcock, New York. $2.75. x + 246. 1946.

Written in direct non-technical language, this is a report of recent achievements in the control of venereal diseases. Due largely to the impetus of the war, increased public interest and greater appropriations have made possible more accurate knowledge as to the extent of the problem and have brought more people under treatment. The work of the Venereal Disease Division of the United States Public Health Service and the results of local programs are described. The relation of incidence to community social problems is emphasized. Improvement in methods of recognition, treatment, and prevention is pointed out.

The problems of the immediate future are discussed in the closing chapters—"Where do we stand?" and "What next?" For continued control and ultimate eradication of these infections, concerted citizen participation and public education are necessities. Attention is also called to the fact that, since communicable diseases do not respect national boundaries, cooperation with the programs of other countries is also an essential matter.

HARRIETTE D. VERA

MUSIC IN HOSPITALS.

By William van de Wall. Russell Sage Foundation, New York. $1.00 (paper). 86 pp. 1946.

This pamphlet includes five chapters: Music in Normal Living; Hospital Organization and Function; the

Hospital Music Program; Integration of the Music Program into the Hospital Service; and the Hospital Musician. The author has written because of the expressed desire of professional musicians and others to make their services available to the sick and in order to describe the use of music in military and mental hospitals. Basic problems encountered in hospital work and the practical use of music programs, teaching of the ill, and other procedures are described, and suggestions are made for a constructive and cooperative use of music in healing.

THE NEW SCIENCE OF SURGERY.
By Frank G. Slaughter. Julian Messner, New York. $3.50. x + 286 pp. 1946.

In this highly readable and extremely entertaining volume, the author has given a concise and authoritative, yet non-technical word picture of the most recent advances in surgery made in World War II, as well as the recent peacetime contributions to the general practice of medicine and surgery. The newest materials and methods employed in immunization against epidemics, in the control of infections, in the treatment of shock, and in the general field of anaesthesia are discussed with clarity and simplicity. Early and adequate attention in handling chest wounds, as well as other internal injuries, is strongly emphasized by the miraculous achievement of the Medical Corps in saving 96 per cent of all the wounded who reached hospitals in World War II, as compared with the dismal record of World War I.

The underlying theme around which the whole fantastic story of modern surgery is built is that of the very close cooperation between the surgeon or physician, on the one hand, and the specialist in the basic sciences of biology, chemistry, physics, or even engineering, on the other.

Since the work has been prepared largely for non-professional readers, the biologist will find many of the discussions over-simplified, and some of the analogies rather far-fetched. For example, in the chapter on psychosomatic surgery, the statement that: "The conflict between her love for the impecunious admirer and her love for the luxury given her by her husband, coupled with lack of sexual attraction between them, has caused an emotional turmoil which has spilled over into the autonomic nervous system and so disturbed the gastro-intestinal tract that the right-sided pain resulted" (p. 233), is certainly a very modest explanation of a highly complex phenomenon. Also, in the chapter on Bundling For Burns, the author states (p. 215): "It was an old-fashioned New England custom of 'bundling' which gave us a new principle in the treatment of one of man's most frequent disasters, 'bundling for burns.'" If the contact in "bundling" had been as intimate as the compression treatment of burns, who knows what the population of New England would have been by now?

There is a table of contents and a short index.

B. AUBREY SCHNEIDER

DENTISTRY. *An Agency of Health Service. Studies of the New York Academy of Medicine Committee on Medicine and the Changing Order.*
By Malcolm Wallace Carr. The Commonwealth Fund, New York. $1.50. xxvi + 219 pp. 1946.

With the collaboration of nineteen leaders of the dental profession, the author has given us a comprehensive survey of American dentistry and its problems. Historical analysis is rudimentary and limited mainly to the problem of dental autonomy. The chapter on education is one of the best parts of the book. Dental practice is ably surveyed in all its aspects, rural, public health, and negro dentistry included. Some important research problems are examined. "Dental Socio-Economics" are dealt with in a rather vague manner, and with a modest allotment of space, strikingly different from the general tenor of this series. The book is primarily a plea for the promotion of dentistry as an independent profession. In this respect it provides much excellent and new information for the layman and the medical man.

ERWIN H. ACKERKNECHT

MOTOR DISORDERS IN NERVOUS DISEASES.
By Ernst Hertz and Tracy J. Putnam. King's Crown Press, New York. $3.00. x + 184 pp. 1946.

This small book is intended to be used in conjunction with a series of teaching films covering the motor disorders. It is pointed out that the major portion of a neurological examination is concerned with the testing of motor functions; consequently, the abnormalities of function are presented in the order in which they might be investigated in an examination.

The sections on involuntary movements, disorders of gait, and disorders of coordination are well covered and illustrated with several pictures which are not always satisfactory, but which are useful within the limitations of the medium of presentation. The anatomical and physiological discussions in each section are brief and clear, being adequate for their intended purpose. The illustrations of methods of examination, especially in the section on muscle status, should be useful to one with more than a passing interest in neurology.

Undoubtedly, access to the companion films would

enhance the value of this work, but standing alone it is a well organized and well presented step from the classroom to the patient.

LOUIS F. CLEARY

PSYCHOLOGY AND ANIMAL BEHAVIOR

PSYCHOLOGY IN EDUCATION.

By James B. Stroud. Longmans, Green and Company, New York, London, and Toronto. $4.00. viii + 664 pp. 1946.

This is an excellent approach to the use of psychology in education. In one of the opening paragraphs, Stroud brings forth the tenet that learning processes proceed best when there is spontaneous seeking to learn and when the instruction is adjusted to the cultural advancement of the people. Stroud reviews quite well the heritages which are correlated to make for our learning processes. The biological and cultural heritages are well expounded, and the author quotes a good deal of literature on the effects of emotions and personality upon learning. Also good are the various tests for the measurement of intelligence, with an excellent list of references that show a careful survey of the literature and a selection of the best and most basic articles.

Stroud derides the current curriculum programs now in use. He rather vigorously denies the very existence of an integrated curriculum, stating that those who postulate "integrated curricula" have only a hazy idea of the significance of a well planned curriculum and associate it with the commonly used phrase, "integrated personality."

This text will serve well as a guide for teachers and students. Stroud has consistently emphasized a socially oriented approach and has shown how our mental processes are improved by education. The text is well written, very lucid, and the index of authors and subjects is excellent.

ROBERT MAZER

TEXTBOOK OF ABNORMAL PSYCHOLOGY.

By Carney Landis and M. Marjorie Bolles. The Macmillan Company, New York. $4.50. xiv + 576 pp. 1946.

This is an excellent textbook on abnormal psychology, presented in a non-dogmatic way. Descriptions of the principal reaction types are followed by chapters on disordered emotion, intellectual deterioration, internal environment, education, and one chapter concerning notable figures and schools in medical psychology and psychotherapy.

This book is well made up, and except for those requiring the specific viewpoint of a physician it could well serve as a textbook of psychiatry. It is thoroughly recommended.

WENDELL MUNCIE

PROGRESS IN NEUROLOGY AND PSYCHIATRY: *An Annual Review.*

Edited by E. A. Spiegel. Grune & Stratton, New York. $8.00. xii + 708 pp. 1946.

With this volume a new series of reviews is launched as an attempt to supplement existing abstract services "by providing critical surveys of the basic theoretical foundations as well as of the various clinical aspects of neurology and psychiatry." The book covers the period from December 1944 to December 1945, and its 39 chapters were written by 53 well selected specialists in their respective fields. Those chapters which may be of particular interest to biologists in general are the following: Neuroanatomy (A. T. Rasmussen); General Neurophysiology (R. W. Gerard and Benjamin Libet); Regional Physiology of the Central Nervous System (P. F. A. Hoeffer); Hearing and Equilibrium (E. A. Spiegel); The Conditional Reflex (W. H. Gantt); Pharmacology of the Nervous System (Louis S. Goodman and James E. P. Toman); Clinical Neurology (J. C. Yaskin and Charles Rupp); Ophthalmoneurology (M. B. Bender); The Autonomic Nervous System (Albert Kuntz); Cerebrospinal Fluid (M. Spiegel-Adolf); Electroencephalography (Herbert H. Jasper and John Kershman); Peripheral Nerve Injuries (J. M. Tarlor), containing an analysis of Russian and German war experiences; General Clinical Psychiatry (S. Bernard Wortis and Lewis J. Sharp); War Neuroses (John P. Spiegel and Roy R. Grinker); Psychosurgery (Walter Freeman and James W. Watts); Group Psychotherapy (S. R. Slavson). On the whole, this annual review is to be welcomed. With subsequent years the foreign literature will become more readily accessible; and new chapters, especially in the psychiatric portion, may be added. Perhaps the practical value of such an annual survey might be enhanced if the different chapters could be published currently as a monthly magazine, similar to the *Fortschritte der Neurologie und Psychiatrie*, edited in Germany since 1929.

WALTER O. JAHRREISS

REBEL WITHOUT A CAUSE. *The Hypnoanalysis of a Criminal Psychopath.*

By Robert M. Lindner. Introduction by Sheldon Glueck and Eleanor T. Glueck. Grune & Stratton, New York. $4.00. xiv + 296 pp. 1944.

Lindner brings before the public a book designed "to

offer for discussion and experiment a psychotherapeutic technique" and "to present the findings of research with a type of personality disorder that is responsible for much of crime and has broad social and even political implications." The book is sub-titled "The Hypnoanalysis of a Criminal Psychopath." Considered just as such, the text stands on its own merit. It is when the author speculates, generalizes, and summarizes that the reader is left with a feeling of doubt about and wonder at the optimism in the claims made.

Lindner introduces the problem of the criminal psychopath from four aspects, the psychological, the physiological, the sociological, and the political. Here little has been contributed to the definition of a psychopathic personality, though an attempt is made to do so through a cursory review of study and speculation to date. The result is as lacking in definiteness as ever. Lindner introduces the method of hypnoanalysis, which he utilizes in his work, briefly presenting aspects of its history and characteristics, and its technique. This is followed by the case material itself, which has been recorded and edited, the latter in an effort to help the reader. This is the part of the text deemed most valuable, since here the attempt is carried out to bring the dynamics of the patient's illness to light. One sees the patient as he works with Lindner and watches him trace back his life situations until they have for him a dynamic significance leading to a degree of insight. All this is done through a period of 46 hours.

Whether or not this may be claimed a "cure" is certainly open to question, so that it is regrettable that no follow-up was reported in the study of this case that would have determined and clarified whatever benefits had been gained, aside from the improvement of ocular symptoms and the immediate insight described. Considering all this, one is again rather overwhelmed by the sweeping optimism of the summary. However, credit is certainly due the author for his interest and enthusiasm in the problem of the criminal psychopath.

It is to be hoped that such investigations as that entered upon by Dr. Lindner here will continue, and that they may eventually lead to a greater understanding of and help for such personalities and the social problem they create.

LUCILLE PRICE

THOUGHT TRANSFERENCE: *An Outline of Facts, Theory and Implications of Telepathy.* *By Whately Carington. Creative Age Press, New York.* $2.50. x + 287 pp. 1946.

One of the chief fears expressed by the English writer of this "outline of facts, theory, and implications of telepathy" is that the reader will reject his explanation because it is too simple. If simplicity is a fault, the reviewer rates the defect in this instance as relatively negligible.

Obviously written for the layman, the discussion of the *facts* of extrasensory perception will undoubtedly seem disappointingly incomplete to the biological scientist. Decrying, with high justification, the scornful refusal of the skeptic even to consider the experimental evidence, Carington then fails to present us with data adequate for a reasonably intelligent evaluation. We are given the alternative of accepting "the basic facts as being absolutely 'cast-iron'" (p. 274) or being branded as blindly prejudiced in our emotional and intellectual preconceptions. Even to the American adherent of "parapsychology," the choice of material may seem curious, with its emphasis on telepathy in contrast to clairvoyance as the established reality, its cavalier treatment of the subject of precognition, and the failure so much as to mention "psychokinesis," the latest and most startling phenomenon described by Rhine and his collaborators. It unfortunately seems to be a matter of: Which source of authority do you prefer?—and even his felicitous stye of writing is insufficient ground for accepting Carington's views.

As to the *theory* itself, it can be more readily stated than understood. In essence, it is based upon the concept of association of ideas, but with the unusual proviso that associations formed in one "mind" are valid for every other "mind," without regard to time or space. In other words, "if an idea A is associated with idea K in my mind, and idea K is presented to your mind, then idea A is more likely to come into your mind than it would be if it had not been associated with K in mine" (p. 232). Of course, one might object that the notion of association is not the clearest explanatory tool of the psychologist, that speaking of it in terms of "psychons" is but a literary translation, that discounting the brain as having "anything to do with it" (p. 185) clarifies the matter little, and that throwing into the reservoir at once all the minds ever existing complicates the issue still further. But at least this formulation has the virtue of accounting for certain telepathic occurrences, and in addition embraces such items as object-reading, ghosts, and localized hauntings. The extent to which the hypothesis simplifies the whole problem is open to debate.

The *implications* of the association theory are far-reaching. Behaviorism and physiological psychology become relatively outmoded in favor of the study of "psychon groups," which incidentally have "no relevant properties other than that of associability, and the strengthening of this by repeated co-presentation" (p. 215), and so are independent of the nervous system. For this last reason, survival after death is unquestionable, if we refer to survival of the psychon system. The nature of this survival can be speculated about, in-

cluding even the imaginary drinking of imaginary whiskey, which produces an imaginary but locally real intoxication and subsequent hangover. The lack of dividing lines between minds leads to a view reminiscent of Jung's "racial unconscious," and has interesting connotations from the standpoints of theology, the social sciences, and government.

It seems doubtful that this book will alter the scientific status of telepathic communication appreciably, and certainly it will cause no great upheaval in the field of biological science.

FRANK W. FINGER

HUMAN BIOLOGY

THE LOST AMERICANS.

By Frank C. Hibben; illustrated by John De Grasse. Thomas Y. Crowell Company, New York. $2.50. xii + 196 pp. 1946.

This popular account tells of the discovery and interpretation of traces of the existence of man in the New World in prehistoric times from possibly about 25,000 to 10,000 years ago. It deals chiefly with the so-called Folsom man and Sandia man, their probable early immigration from eastern Siberia and their roles as ancestors of the American Indians. The author, who himself participated in some of the field work, writes with enthusiasm, imagination, and great ability. He describes vividly the fascinating search for early man in this continent and uses the meagre yet important results of this search in constructing a coherent, though necessarily tentative, story which will appeal to the layman and young student without arousing more than a few, detailed objections on the part of the conservative expert.

This little volume is well adapted to recruit new students of this first chapter in American history. Only when there are a greater number of informed people searching for "Lost Americans" can we reasonably expect to find bodily remains of these earliest immigrants, in addition to the samples of their crude workmanship discovered so far.

A. H. SCHULTZ

THE ARCHAEOLOGY OF BONE CAVE, MILLER COUNTY, MISSOURI. *Anthropological Papers of The American Museum of Natural History, Volume 40, part 2.*

By E. Adamson Hoebel. The American Museum of Natural History, New York. 50 cents (paper). Pp. 135–158 + 5 plates. 1946.

Results of a limited excavation in the Bone Cave site, in the summer of 1943, are presented here. Of the many caves in the Ozark limestones, this one had been known as the bone cave because of the reported finding of many human bones on the floor of the cave by early settlers. The principal reason for excavating it, however, was due to its relative dryness, the depth of its deposits, and its relatively easy access. It was not a "dry" cave in the usual sense, for a spring keeps the deposit quite wet, and no perishable material survived.

Material recovered was of stone, bone, shell, and pottery. This material is described, and characteristic examples of artifacts are illustrated. Despite the reputed frequency of human bones, virtually none were recovered.

The black upper layer, up to four feet deep, yielded evidence of three early phases of Woodland culture. There was no evidence of later Woodland cultures. Significant shifts in projectile points and in pottery were found. Pottery was rare in the bottom level, and common in the upper level. The author notes that caves in the southwestern part of Missouri have yielded evidence of a differing, cruder, and probably earlier culture than that of the Bone Cave. It is, therefore, important to note that the author was unable to carry the excavation of the cave to completion, but dug only the uppermost layers. He estimates that the floor of the cave lies at least eight feet below the deepest excavation. The Woodland occupational material overlies a sterile gumbo clay. The possibility of earlier cultures being represented at a greater depth seems rather good, and the importance of testing this cave further for its possible contribution of an important stratigraphic sequence is obvious.

GEORGE F. CARTER

THE TCHEFUNCTE CULTURE, AN EARLY OCCUPATION OF THE LOWER MISSISSIPPI VALLEY. *Memoirs of the Society for American Archaeology. Supplement to American Antiquity, Volume X, Number 3, Part 2, 1945.*

By James A. Ford and George I. Quimby, Jr., with an appendix on the skeletal remains by Charles E. Snow. The Society for American Archaeology and Louisiana State University Press, Menasha, Wisconsin. $1.50 (paper). xii + 113 pp. + 12 plates + 3 tables. 1945.

The Tchefuncte culture of the lower Mississippi valley is related geologically to the recent deltas of the Mississippi River, as worked out by R. J. Russell. It is the earliest known occupation of this area, and is related to the Archaic culture of the Southeast and to similar cultures of the Middle Mississippi valley. The culture is characterized by considerable simplicity. The earliest phases apparently represent a simple hunting, gathering, and fishing life.

The authors divide the culture chronologically into

three periods. The earliest period had no pottery, the later periods added pottery and, the authors think, possibly agriculture. The two later periods are differentiated on the basis of several traits, the most important of which are pottery type differences.

The relation of these sites to the sequence of delta shifts worked out by Russell is of considerable interest. The extension of some of the middens below sea level also owes its proper evaluation to the careful study that has been made of the geology of the delta. Such work shows clearly the interdependence of the various sciences, and, particularly, the dependence of archeology on other sciences for much of its chronological interpretation. The authors have done an excellent job in relating their material to the surrounding regions and in showing its place in the cultural development of North America.

There is an appendix on the skeletal material recovered. (Relatively little skeletal material was recovered: 31 male skulls, 21 female.) The population was related to the early dolichocephalic Amerind, but shows variation toward the later brachycephalic types.

GEORGE F. CARTER

THE SOCIAL CULTURE OF THE NUNIVAK ESKIMO. *Transactions of the American Philosophical Society Held at Philadelphia for Promoting Useful Knowledge. New Series—Volume XXXV, Part III.*

By Margaret Lantis. The American Philosophical Society, Philadelphia. $2.50 (paper). Pp. 153–323. 1946.

Nunivak is an isolated island in the Bering Sea. Margaret Lantis lived in Nunivak for one year (1939–40) and was just in time to study this example of Eskimo culture before it underwent rapid change. Nunivak culture has much in common with other Eskimo cultures, but being Alaskan, it differs from the "classic" Greenland-Central Eskimo type. A more moderate climate and a more regular food supply give it less harsh features ("healthier" ones, says Miss Lantis). There are fewer accidents; there is less poverty, less cold. Religion is more formal, and not so inspirational as in other Eskimo cultures. On Nunivak life runs, in Eskimo fashion, in sharply defined seasonal cycles, and is surrounded by numerous taboos. There is a wealth of recreational methods (whether this is as typically Nunivak as the author thinks, might be doubted). The main feature of ceremonial life is the Bladder feast, described in detail by the author. Social life is individualistic and amorphous in the Eskimo way, though somewhat structured through institutions like the man's house, joking relationships, and partnerships. Adoption is very common. The author has prepared an intelligent monograph, rich in data and well written.

ERWIN H. ACKERKNECHT

LINGUISTIC STRUCTURES OF NATIVE AMERICA. *Viking Fund Publications in Anthropology, Number Six.*

By Harry Hoijer, L. Bloomfield, M. R. Haas, A. M. Halpern, F. K. Li, S. S. Newman, M. Swadesh, G. L. Trager, C. F. Voegelin, and B. L. Whorf. The Viking Fund, New York. $4.50 (paper). 423 pp. 1946.

After a good introduction by Hoijer, 13 studies by 10 authors on the linguistic structure of Eskimo, Apache, Algonquian, Delaware, Hopi, Taos, Yokut, Yuma, Tonkawa, Chitimacha, Tunica, Chipewyan, and Aztec languages are presented. The title is a misnomer as, except for the last, all languages analysed are North American. The book very ably continues the work started by Franz Boas in his *Handbook of American Indian Languages*. The Viking Fund is to be complimented for having saved from oblivion this most valuable manuscript, planned by the late Edward Sapir.

ERWIN H. ACKERKNECHT

SOME NOTES ON THE ARCHAEOLOGY OF THE DEPARTMENT OF PUNO, PERU. *Expeditions to Southern Peru, Report Number 3. Papers of the Peabody Museum of American Archaeology and Ethnology, Harvard University, Volume XXVII—Number 3.*

By Marion H. Tschopik. Peabody Museum of American Archaeology and Ethnology, Harvard University, Cambridge. $1.65 (paper). x + 57 pp. + 10 plates. 1946.

Mrs. Tschopik accompanied her husband in his field work in the Andes about the Titicaca Basin. Her interest centered in the archeology, and when opportunity offered, she visited archeologic sites in the area and collected sherds and other materials. Particular attention was paid to the Chullpas of the area.

These structures, often round, usually of stone, have had various uses attributed to them. The author's conclusions that they were burial places seems fully justified. The structures are divided into four architectural types. They are found to have, in part, differing geographical distributions and to differ somewhat in time. Some precede Inca influence in the area; others seem to have been built after the Inca conquest of the area. Thus, there is no one "Chullpa period," but rather chullpas were being built during several periods.

Sherds, amassed mostly from reconnaissance and surface collecting from many sites, including the chull-

pas, were studied, and an attempt was made to place them in relation to the known cultures north and south of the Titicaca area. Such typological studies have been made before in the Andean region, and the results are often good. The sherds, like the chullpas, show that there are several periods represented and that there is no justification for the use of such a term as the "Chullpa period." The material is both *pre* and *post* Inca, and much of the material represents the local cultures in the area during the period between the Tiahuanaco-Pucara and Inca influences.

The author describes her pottery types and arranges them in suggested orders. She stresses that the sequence is not based on stratigraphy and that her allocations in time are meant merely as suggestions. Despite its tentative nature, her work is a distinct contribution.

GEORGE F. CARTER

BRAZIL: *People and Institutions.*
By T. Lynn Smith. Louisiana State University Press, Baton Rouge. $6.50. xxiv + 843 pp. + 1 plate. 1946.

This is by far the most substantial book on Brazil published so far in English. That it was written by a rural sociologist makes for emphasis on certain aspects of Brazilian life. But such a selection is less arbitrary in the case of Brazil, a still overwhelmingly rural country, than it might be in the case of other countries.

Brazilian agriculture is to a large extent "fire agriculture," and uses the old Indian methods of tilling the soil. Only 15 per cent of Brazilian farms are provided with plows. Socially Brazil, founded as a country of enormous latifundia worked by slaves, was and is closer to our South than to its "mother-country" Portugal, which is characterized by its small farms. Prevalence of the big estate might to a large extent explain many perplexing traits in Brazilian culture, such as the very low standards of living and health (widespread malnutrition), the illiteracy of over 60 per cent, the exceptionally high rate of illegitimate births, and the migratory habits and other attitudes of the rural worker. Brazil is still "only occupied, not yet settled." Only during the last century have farms, and consequently a middle class, developed, mostly in the Brazilian South, which thus more and more tends to assume political leadership.

Besides the agrarian question in all its aspects (techniques, land division, settlement patterns, etc.) the author gives a thorough examination to vital statistics. In Brazil's impressive population increase between 1920 and 1940 (36 per cent), the role of immigration was minimal. The main factor has been a birth rate of 38, the effects of which not even a death rate twice that of the U. S. can entirely eliminate.

In his discussion of Brazilian institutions, the author has emphasized the enormous cultural and racial diversity of the country. Less exclusively absorbed by the Negro problem than other North American students of Brazil, Smith rightly stresses the Indian component as a major element along with the Portuguese and African in the cultural and racial setup. He gives extremely interesting data on widespread African cults in an officially Roman Catholic country. The author's strictly negative attitude towards the Japanese element seems little justified by actual experiences.

Besides extensive statistics, the author quotes a great many times from Brazilian authors. In view of our little familiarity with Portuguese, these quotations greatly enhance the value of the book, which aside from that deserves a lot of superlatives for its rich documentation, and its intelligent, fearless, and balanced analysis. To me it also made most fascinating reading. Yet I feel that its bulk and its somewhat clumsy organization may render it inaccessible to the great mass of our countrymen, who ought to know the essential data on Brazil and the opinions of the author concerning so vital a subject to us as the greatest country of South America. Thus some sort of an epitome of this standard work might be very useful and desirable.

ERWIN H. ACKERKNECHT

THE PEOPLES OF MALAYSIA. *Second Printing.*
By Fay-Cooper Cole. D. Van Nostrand Company, New York. $4.00. xiv + 354 pp. + 37 plates. 1945.

This moderate-sized ethnographic textbook contributes a comprehensive picture of the history, mode of life, culture, migrations, and probable origins and relationships of the peoples inhabiting the Philippines, Borneo, Sumatra, Java, the Malay Peninsula, and some of the smaller islands of that region. The author has devoted years of field work and most of his research activities to the anthropological problems of Malaysia. He has succeeded in outlining the story of mankind in the Malaysian countries not only for the professional anthropologist, but also for the general reader interested in Far Eastern affairs. The former will welcome specially the 41 pages of technical notes in the appendices and the generous bibliography, and the latter will be grateful for this reliable and readable volume and particularly for the author's thoughtful conclusions in regard to the future of the Malaysian peoples. Biological readers of this, as of so many other anthropological books, will be impressed by the wealth of the available, thorough, and detailed information appertaining to human culture and social organization, including every conceivable product of man's mind and hands, and with the contrasting great dearth of significant data relating

to morphological and physiological qualities which could and should furnish the decisive evidence in problems of racial origins and relationships. Little improvement in this state of affairs can be expected until physical anthropology has become more fully and competently represented in our scientific institutions. Even though the author himself has contributed a large amount of valuable new data appertaining to the physical qualities of the peoples of Malaysia and gives due attention and space to what is known of the bodily features of the human groups he discusses, he has far more to say about, e. g., the very scanty clothing of pygmies than about their bodies. Soon even the remnants of some of these highly interesting groups of pigmies will have disappeared, and yet we still know little of their biological qualities beyond stature, skin color, hair form, shape of head, and a few other characteristics. The manufacture and use of their weapons, and their customs and beliefs relating to birth and death have been fully recorded, but there exists no accurate information at all regarding the proportionate length of their limbs, the sequence of their tooth eruption or their epiphyseal union, their blood groups, their ages at maturity, their sex ratio, the relative weights of their endocrine glands, and many other physical traits.

This book belongs to the best we possess to-day on its subject, but it leaves a great many questions relating to the peoples of Malaysia unanswered, a continuing challenge for future work.

A. H. SCHULTZ

CHINESE FAMILY AND SOCIETY. *Published under the auspices of The International Secretariat, Institute of Pacific Relations, and The Institute of Social Research.*

By Olga Lang. Yale University Press, New Haven. $4.00. xviii + 395 pp. 1946.

This very thorough study of the changes in the character of Chinese family life under the impact of westernization and industrialization makes an admirable complement to the two studies of Chinese village life recently reviewed in this journal (see Martin Yang, *A Chinese Village*, Q.R.B. 21: 215; and H. T. Fei, *Peasant Life in China*, Q.R.B. 21:422. 1946). Whereas Yang portrayed a village where little has changed and the problems are chiefly agricultural, and Fei described a village where industry has become an important aspect of life, Olga Lang has adopted a comparative treatment, with emphasis upon data gathered in the big cities, particularly in Peiping and Shanghai. The youth of the country play a predominant role in her analyses of changing relationships. There are no startling surprises for anyone who knows China, but to the contrary a record of steady trends accentuated by foreign influences. These trends can often be traced back into medieval China, or even into ancient times. These roots are considered in Part I of the book, on "The Family in Old China" (pp. 1–58). The author succeeds in showing that the so-called typical "joint" family in China was never really prevalent, even in olden times. Today the smaller conjugal family, made up of husband, wife, and children, is by far the commonest sort of family, especially in cities and in the poorer economic strata of the population. The clan, in most parts of China, is obsolescent and rapidly decaying. The independence of the youth and particularly of the women is steadily increasing.

The author can write well, and sometimes does, but the weight of her statistics is often too much for vigor and freedom of style. As to substance, no one will criticize.

BENTLEY GLASS

MY AFRICA.

By Mbonu Ojike. The John Day Company, New York. $3.75. xiv + 350 pp. + 8 plates. 1946.

Mbonu Ojike grew up in a Nigerian village among 18 brothers and 31 sisters, his father having 10 wives. At the age of 16 he went to normal college, and in 1938, at the age of 22, he left Africa to continue his studies in the United States. The first quarter of his book is filled with a description of these early years. For the general reader this forms an excellent introduction to the more theoretical second part, and the anthropologist will welcome it as a valuable document on acculturation.

The second part of the book gives an enthusiastic description of native African economic, social, marital, religious, aesthetic, and political life; and a third part is a vigorous plea for African freedom and cooperation in a brotherly world. The second part is, of course, highly rhetorical and as little objective as corresponding patriotic treatises of Western scientists on their own countries. Besides any correct statements on actual values in African life, there is a lot of embellishment, wishful thinking, and inaccuracy—very often resulting from the fact that the author simply identifies Nigerian traits with African in general. While, therefore, this part can be used only with caution as factual information, as the expression of the feelings of the African intelligentsia it should be studied very carefully by all concerned. In view of the unconscionable behavior of our race in Africa and elsewhere, we must be glad that the author's conclusions are not more embittered and aggressive.

ERWIN H. ACKERKNECHT

MYTHS AND SYMBOLS IN INDIAN ART AND CIVILIZATION. *The Bollingen Series VI.*

By Heinrich Zimmer. Edited by Joseph Campbell. Pantheon Books, New York. $4.50. xiv + 248 pp. + 32 plates. 1946.

In these lectures the late refugee scholar whose premature death is so much to be deplored has skillfully used Indian mythological texts and works of art to introduce the reader into the fundamental conceptions of Hindu thought. Though these appear entirely different from our Western thought, in some points one is struck by strange coincidences with our latest physical theories. Zimmer illustrates the Hindu idea of time, which is a denial of time in our sense, by some very significant legends. He describes the mythology and main symbols of the three highest gods, Vishnu, Shiva, and Kali, who incorporate simultaneously the basic principles of creation and destruction. The author insists on the fundamental similarities of Indian thought in its preVedic, Brahmanistic, and Buddhistic forms. This approach, along with many details and interpretations, and a particularly sympathetic attitude towards the Hindu viewpoint make up Zimmer's own contribution in a field which otherwise has been covered already in a great many scholarly treatises. The somewhat dramatic character of the lectures, which has been preserved in the book, makes it an excellent introductory volume.

ERWIN H. ACKERKNECHT

POPULATION IN MODERN CHINA.

By Ta Chen. The University of Chicago Press, Chicago. $2.50. x + 126 pp. 1946.

China is today inhabited by about one-fifth of the entire world's population. Though population estimates of China have been recorded since early days, an accurate and detailed census exists at present for less than one per cent of the total population. The latter modest but reliable census figures, including particularly the recent Kunming Lake region census, form the basis for this scholarly analysis, which supplies a much needed demographic picture of modern China.

The 77 pages of text give a brief critical survey of China's historical population data, describe the methods and difficulties of obtaining census data in China, and discuss the composition of the population according to sex, age, and occupation, the rates of births, deaths, and marriages, the density and increase of population, and the prevalence of recent migrations. Many additional topics are considered and supported by at least some statistics. Thus there are brief sections on causes of death, on frequency of physical and mental deficiencies, on fertility according to age and occupation, age at marriage, average size of farms and land tenure, handicrafts, etc. A brief final chapter deals with population policies for the future and, particularly, with the relevant views of the late Dr. Sun Yat-Sen. The text is fully documented by 65 tables collected in an appendix of 45 pages. The main findings for China are compared with corresponding data for many other countries.

This little volume contains a wealth of information of interest to sociologists, economists, and anthropologists. The latter will find not only new data on human biology, but many incidental notes on Chinese customs. There is no summary and no general conclusions are given, however. Of the numerous and varied findings, the following sample may be quoted here: "China has quite a low rate of natural increase, 5.0 persons per 1,000 population per year. If she intends to keep this low level of natural increase, it is really unnecessary to have such high birth rates and high death rates as she now has." It is going to require much more than good intentions to regulate the increase in population and to avoid the "unnecessarily" high birth and death rates!

A. H. SCHULTZ

BIOMETRY

UNITED STATES LIFE TABLES AND ACTUARIAL TABLES 1939–1941. *Sixteenth Census of the United States: 1940. United States Department of Commerce, Bureau of the Census.*

By Thomas N. E. Greville, prepared under the supervision of Halbert L. Dunn. United States Government Printing Office, Washington. $1.25. iv + 153 pp. 1946.

Interest in the longevity of the population, both on the part of scientists and the general public, is very great and has been for centuries. Any new evidence on the subject is therefore always welcome. Official life tables for this country were first published after the 1910 census, one of the publications of that time including tables for 1890, 1901, and 1910. Since then life tables have been prepared after each decennial census.

The present volume contains life tables based on population figures from the 1940 census and deaths in the period 1939 to 1941. The tables, prepared by Thomas N. E. Greville, Actuarial Mathematician in the Census Bureau, represent one of the finest volumes put out in this series or that of any other country. The introduction, summarizing some of the principal findings, and the explanatory text, written for demographers, public health workers, and other applied people without actuarial training, are very well presented. The only important deficiency in the tables is that the raw data on which the computations are based have been omitted. Since various decisions

must arise in abstracting the data from the official volumes, it is unfortunate that these basic tabulations are missing. This material was also omitted from the 1930 tables, and it is hoped that the decision to eliminate the basic observations from the life table volume will not be maintained in future publications.

There are 12 life tables presented, the functions in every case being tabulated for each year of life. The groups for which tables have been prepared are: total population, population specific for sex, population specific for race (white, Negro, and other races), and population specific for sex and race. Each table is based on data for the entire continental United States. There are also certain actuarial tables included for use in calculating premiums and benefits in connection with insurance and annuities, and explanatory sections presenting some of the theory and use connected with the actuarial tables, as well as an account of the method of life table construction that has been used.

The many interesting comparisons that might be made from this material are too extensive for brief review, and only one will be mentioned, that of the age to which 50 per cent of the people would survive according to the prevailing mortality rates. For the total population of the United States in 1940, this is 70 years of age. That is, the mortality risks of 1940 are such that half of the people, living according to those rates, would survive to ages beyond 70. The enormous improvement in mortality at the younger ages in this country is indicated by the fact that the corresponding figure for 1901 was only 58 years. The differences between white and Negro survivorship at the present time, for the 50 per cent position, is practically the same as that for the total population between 1940 and 1901. "Other races," given for the first time in this volume, show a survivorship intermediate between that of whites and Negroes.

An innovation in these tables, appreciated by this reviewer, is the presentation of the q_x column ahead of the l_x column. Since this is the order of computation it seems more logical than the conventional order, and has definite advantages from the teaching point of view. This change, as well as the new approach in the text discussion, indicates a fresh point of view for which the author of this set of tables is to be particularly commended.

MARGARET MERRELL

MATHEMATICIAN'S DELIGHT. *Pelican Books.* *By W. W. Sawyer. Penguin Books, New York.* 25 cents (paper). 215 pp. 1946.

This is an attractive little book to place in the hands of students. The topics treated range from arithmetic and algebra to graphs, trigonometry, and calculus. The final chapter delivers a well placed fillip to that four hundred year old tool, the square root of minus one. There is a chapter on "ways of growing," but the biologist will regret the omission of statistics. The style of the book is planned for those without mathematical training. Now that the war is over, it is to be hoped that these very useful Pelican Books will appear on better paper while maintaining the same price.

DE OMNIBUS REBUS ET QUIBUSDEM ALIIS

SCIENTIFIC, MEDICAL, AND TECHNICAL BOOKS. *Published in the United States of America 1930–1944: A Selected List of Titles in Print with Annotations. Edited by R. R. Hawkins. Prepared under the direction of the National Research Council's Committee on Bibliography of American Scientific and Technical Books. The National Research Council, Washington, D. C.; R. R. Bowker Company, New York (domestic orders); United States International Book Association, New York (foreign orders).* $20.00. xvi + 1114 pp. 1946.

This monumental reference work contains listings of over 5000 books written by citizens of the United States and Canada and published in the United States within the fifteen years covered. Many of the important monographs, papers and proceedings of scientific and technical societies are also included, although the survey of these could not be complete. College textbooks are included, but high school and elementary texts have been omitted.

The books are classified by subject and topic, ordered alphabetically by author under each topic, and numbered serially throughout the volume. Title, publisher, date, number of pages, illustrations, standing height, and price are given, followed by a condensed Table of Contents, and, in most instances, by a Note on the general purpose and character of the book, important changes in the latest edition, etc.

Appendices list the state agencies in the United States that issue publications in geology, engineering, and agriculture, and a directory of publishers. The Author Index fills 45 triple-column pages, the Subject Index 26 double-column pages; both indices refer to titles by serial numbers. It is very easy to find any title quickly.

An idea of the size and selectiveness of the list may be obtained by comparing the number of books listed under the subjects Natural History, Biology, Botany, Zoology, Man, Human Anatomy, Physiology, Biochemistry, Bacteriology, Medicine, Gynecology and Obstetrics, Surgery, Dentistry, Aviation Medicine, Industrial Medicine, Military and Naval Medicine, Public Health, Nursing, Hospitals, First Aid, Personal Hygiene, Psychosomatic Medicine, Psychiatry, Mental Hygiene, and Psychology collectively, with the number

of books and monographs reviewed in the *Quarterly Review of Biology* over the same period of fifteen years. *Scientific, Medical, and Technical Books* lists 1946 titles in the above categories. The *Quarterly Review of Biology*, which excludes the more technical and clinical medical books and includes more elementary books and new editions, has over the same period reviewed approximately three times the above number.

While the present reference volume has been prepared chiefly as a guide to our scientific literature for international use, it will undoubtedly prove to be a most useful tool for book selection in this country as well. Libraries will find it indispensable. Its usefulness is greatly enhanced by the painstaking care with which it has been produced. In spite of its size, it is virtually free of typographical errors.

BENTLEY GLASS

GERMAN-ENGLISH SCIENCE DICTIONARY *for Students in Chemistry, Physics, Biology, Agriculture, and Related Sciences. Second Edition.*

By Louis De Vries, with the collaboration of members of the Graduate Faculty, Iowa State College. McGraw-Hill Book Company, New York and London. $4.50. xiv + 558 pp. 1946.

Enlarged by about 50 per cent over the first edition, particularly in the number of chemical terms, this dictionary will certainly continue to be a mainstay of the young scientist beginning to master German. For the biologist its chief deficiency continues to be the absence of many of the names of animals, plants, and structures one is likely to meet in scientific literature; but the reference work is very useful, nonetheless. There is a 15-page list of German abbreviations at the end of the book, together with a conversion table, atomic table, thermodynamic symbols, electric units of measure, abbreviations of periodicals (non-biological), lists of measurements, and geographic names.

FORMULAIRE TECHNIQUE DU GEOLOGUE. *Ce qu'il faut Savoir sur l'Enseignement, l'Observation sur le Terrain, la Récolte, l'Étude et la Conservation des Roches et des Fossiles. Savoir en Histoire Naturelle, Volume XIII. Guides Techniques du Naturaliste, Volume IV.*

By Raymond Furon. Paul Lechevalier, Paris. 80 fr. (paper). 214 pp. 1943.

The general contents of this pocket-size volume are indicated in its extensive title. Designed for the French reader, and apparently in particular for the Parisian, the work outlines the courses of study in geological sciences at the various universities and colleges in Paris, lists the geological collections open to the public in that city, gives a list of French geological societies and their publications, and a similar list of French colonial geological publications and most recent maps. Then follow: a discussion of geologic maps, sections, etc., with a description of geologic equipment and its uses; descriptions of eight local excursions to localities exhibiting various types of geologic phenomena, with notes on the data and field relationships to be observed and a discussion of their interpretations; a chapter devoted to the development of a geologic laboratory and the organization of its collections; another, to the rocks and rock-forming minerals, their classification and methods of study, both megascopic and microscopic; and, finally, forty-four pages given to a discussion of the collection, preparation, and determination of fossils. Up-to-date, but very brief bibliographic references document the various discussions.

Any consideration of the vast field that the author attempts to cover in so small a volume must leave the reader amazed at the amount of information he has managed to include. Yet it is obviously far from complete or even adequate, for any one phase of the subject. In general, the techniques described are of standard, long-known, kinds; many of relatively recent development, which are widely used in America at least, are conspicuously absent. The French (and especially the Parisian) amateur may find much of value here; the geologist need not be much concerned with it.

H. E. VOKES

A TREASURY OF DOCTOR STORIES *by the World's Great Authors.*

Compiled by Noah D. Fabricant and Heinz Werner. Frederick Fell, New York. $3.00. xvi + 493 pp. 1946.

This is a collection anyone should enjoy for the good things that are in it. It is true that some of the selections raise doubt as to the reasons for their inclusion, but on the whole the compilers have been discriminating in a literary as well as in a professional sense. The stories and excerpts—some of the latter ending all too abruptly—succeed in portraying many facets of the art and science of healing, from the standpoint, to be sure, of the literary artist and non-scientist rather than from that of the doctor himself. Perhaps this collection is best regarded as a welcome complement to that rapidly lengthening shelf of books wherein doctors reminisce about their experiences, some wittily, some tediously, and many with great illumination. But, I am sure, none of the reminiscences have a character at all like that of a number of the selections in this "treasury," such as Doc Mellhorn's report from the Pearly Gates (Stephen Vincent Benét), or Doctor Harvey Herbert's account of his neurotic Aunt Emma and her will (Don Marquis).

BENTLEY GLASS